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STATISTICAL ANALYSIS PLAN (SAP)

FOR

PROTOCOL OOC-ACM-303

A phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate safety and efficacy of octreotide capsules in patients who previously tolerated and demonstrated biochemical control on injectable somatostatin receptor ligands (SRL) treatment

November 29, 2017
Version 7.0

Sponsor:
Chiasma, Inc.
[redacted]

SIGNATURE PAGE

STATISTICAL ANALYSIS PLAN (SAP) FOR PROTOCOL OOC-ACM-303

A phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate safety and efficacy of octreotide capsules in patients who previously tolerated and demonstrated biochemical control on injectable somatostatin receptor ligands (SRL) treatment

Approvals:

[redacted]

Signature Date

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Signature Date

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1 Introduction

This Statistical Analysis Plan (SAP) contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis. This SAP should be used in conjunction with the protocol. If there are any discrepancies between the protocol and SAP, this SAP will prevail. Any deviations from this SAP that are implemented in the final analysis will be documented with sound clinical and statistical rationale in the Clinical Study Report (CSR). In the event of any changes to the primary endpoints or analyses, these changes will be documented through a protocol amendment, consistent with ICH E9.

2 Study Objectives and Hypotheses

2.1 Primary Objective

To assess maintenance of biochemical control with octreotide capsules compared to placebo in patients with acromegaly, who previously demonstrated biochemical control on SRLs.

2.1.1 *Primary Hypothesis*

The primary hypothesis of the study is that treatment with oral octreotide results in a greater proportion of patients maintaining biochemical control than treatment with placebo.

2.2 Secondary Objectives

The following are secondary objectives:

- To assess maintenance of biochemical control, based on GH, with octreotide capsules compared to placebo
- To evaluate the safety profile of octreotide capsules compared to placebo

2.2.1 *Secondary Hypotheses*

The secondary hypotheses of the study are:

- Treatment with oral octreotide results in a greater proportion of patients maintaining biochemical control, based on GH, than treatment with placebo.

2.3 Open Label Extension Objectives

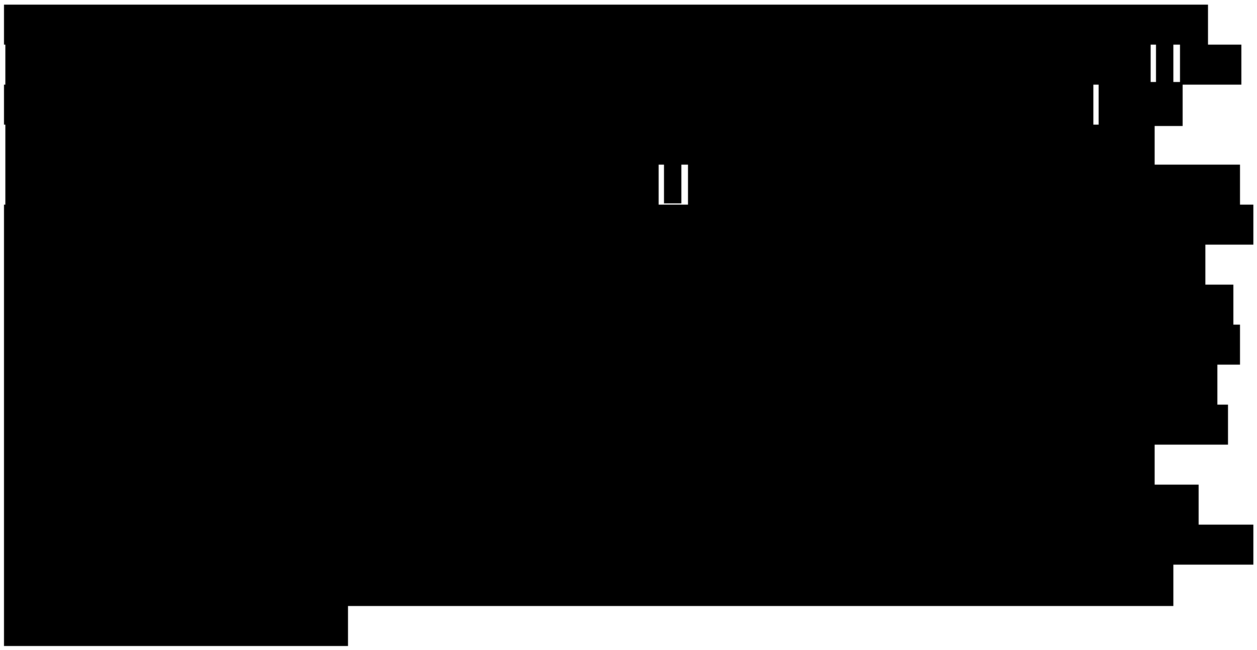
The objective of the open label extension is to assess the long-term safety and efficacy of octreotide capsules in acromegaly patients.

2.3.1 *Open Label Extension Hypothesis*

Not applicable.

3 Study Design

This will be a phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the safety and efficacy of octreotide capsules in acromegaly patients who previously tolerated and demonstrated biochemical control on injectable SRL treatment.



Patients meeting the pre-defined withdrawal criteria, IGF-1 ≥1.3×ULN AND exacerbation of acromegaly clinical signs or symptoms compared to baseline, for 2 consecutive assessments, while treated for at least two weeks with 4 capsules per day, during the DPC period, will be rescued with injectable SRL treatment used prior to Screening and will continue to be followed per protocol until week 36. At week 36, these patients will be offered to enter the OLE period and receive octreotide capsules. Patients who do not complete the full 36-week DPC period will not be eligible to enter the OLE period and will not require further follow up beyond week 36.

Patients who discontinue study medication early during the DPC period for reasons other than the pre-defined withdrawal criteria, should continue to be followed per protocol until week 36. The Sponsor recommends re-initiation of their prior injectable SRL treatment (as rescue or escape mediation) upon meeting the pre-defined withdrawal criteria described above. These patients will not be eligible to enter the OLE period and will not require further follow up beyond week 36.

Patients who discontinue study medication during the OLE period, for any reason, or have completed the 36-week DPC period on study medication and are ineligible or not opting to continue into the OLE period, will revert to their prior injectable SRL treatment (prior to Screening) or other treatment as determined by their physician. These patients will be followed-up for 12 weeks after end of treatment (EOT).

Database lock for the DPC period will occur after the last patient completes the DPC period. At this timepoint, the study will be unblinded and all data from the DPC period analysed. Interim analyses of the OLE period will be conducted periodically, after completion of the DPC period. Data collected post DPC period (week 36) in patients not entering the OLE period and those who entered the OLE period will be included in the OLE database.

3.1 Randomization

Eligible subjects will be randomized 1:1 to octreotide capsules or placebo using permuted block randomization. Randomization will be stratified by prior SRL dose (Low vs Middle or High)

SRL Injection Dose	Dose Level Category
Octreotide dose of 10 mg q4w Lanreotide dose of 60 mg q4w or 120 mg q8w	Low
Octreotide dose of 20 mg q4w Lanreotide dose of 90 mg q4w or 120 mg q6w	Middle
Octreotide dose of 30 mg q4w Lanreotide dose of 120 mg q4w	High

3.2 Sample Size

Approximately 50 patients will be enrolled into the DPC period of the study on either octreotide capsules or matching placebo, in a 1:1 ratio.

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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

4 Analysis Sets

4.1 Full Analysis Set

The Full Analysis Set (FAS) is defined as all randomized patients. This population will serve as the primary efficacy analysis population for the DPC period of the study. Patients will be included in the group to which they were randomized.

4.2 Per-Protocol Set

The per-protocol (PP) set will consist of all subjects in the FAS set who were compliant with study medication, and do not have any major protocol violation (e.g., administration of a prohibited concomitant medication, violation of inclusion/exclusion criteria, non-compliance with study medication). Protocol violations that will exclude a subject from the PP set will be identified prior to breaking the blind. This set will be used to assess efficacy and will provide support to the primary analyses with the FAS set.

4.3 Safety Set

The safety set will consist of all randomized subjects who received any amount of study medication. Assuming no dosing errors, the safety set will be the same as the FAS. The safety set will be used for all safety analyses. Subjects will be assigned to a treatment group based on the treatment they received. Therefore, if a subject received octreotide at anytime during the DPC period, they will be included in the octreotide group for safety analyses.

4.4 Open Label Extension Sets

For the OLE phase, several different analysis sets will be defined.

1. The open label extension (OLE) set will consist of all patients enrolled into the OLE phase of the study who receive at least one dose of open label study drug.
2. Octreotide capsulepatients from the DPC period who enrolled into the OLE phase and received at least one dose of open label study drug (OLE-OCT)
3. Octreotide capsule patients from the DPC period, who were classified as treatment responders based on the primary endpoint, at the end of the DPC period, and who enrolled into the OLE phase and received at least one dose of open label study drug (OLE-OCT-RESP).

5 Analysis Endpoints

5.1 Efficacy Endpoints

5.1.1 *Primary Efficacy Endpoint*

The proportion of patients who maintain their biochemical response at the end of the DPC period. Maintenance of response will be defined by using the average IGF-1 level of the last 2 available assessments [redacted] in the DPC period [redacted]. If the average IGF-1 is ≤ 1×ULN, a patient will be classified as a responder (i.e., maintained their biochemical response). If the average IGF-1 is > 1×ULN, a

patient will be classified as a non-responder. Patients who discontinue study medication during the DPC period for any reason will be classified as non-responders for the primary analysis, regardless of their IGF-1 values.

5.1.2 *Secondary Efficacy Endpoints*

1. Proportion of patients who maintain GH response (i.e., GH < 2.5 ng/mL) at week 36, out of those who were responders (i.e, GH < 2.5 ng/mL) on SRL injections at Screening. GH response will be defined using the mean integrated GH value, based on 5 assessments, 30 minutes apart. Patients who discontinue treatment during the DPC period for any reason will be classified as non-responders for the GH response analysis, regardless of their GH values.

2. Time to loss of response: Loss of response is defined as the earliest time when the IGF-1 of 2 consecutive visits is > 1×ULN, after the patient is treated for at least 2 weeks with 4 capsules per day. The date time of the earliest of the 2 consecutive measurements will be used. To account for patients who prematurely discontinue treatment prior to meeting these criteria, three different approaches will be used (i.e, this endpoint will be defined in threre different ways). The three different defintions that will be used are as follows; (A) they will be counted as having had an event (i.e., met the criteria) at the time of treatment discsontinuation; (B)they will be censored at the time of their last available assessment, when the patient was known to have not lost response. If there is no post-baseline assessment for response status, the patient will be censored with a time to loss of response of 0; and (C) they will not be censored, but evaluated for response based on the data collected after discontinuation (i.e, as long as the patient is known to be a responder regardless of adherence to treatment. For all three approaches patients who complete the study without meeting these criteria will be censored at their last study visit during the DPC period (i.e., week 36). Although 3 different approaches will be used, only the first approach will be used with respect to determining success. The other 2 approaches will not be considered in the multiplicity adjustment and are considered exploratory.

3. Time to loss of response: Loss of response is defined as the earliest time when the IGF-1 of 2 consecutive visits is > 1.3×ULN, after the patient is treated for at least 2 weeks with 4 capsules per day. The date time of the earliest of the 2 consecutive measurements will be used. To account for patients who prematurely discontinue treatment prior to meeting these criteria, three different appraoches will be used (i.e., this endpoint will be defined in three different ways). The three different defintions that will be used are the same as those outlined for the endpoint above (endpoint #4). Patients who complete the study without meeting these criteria will be censored at their last study visit during the DPC period (i.e., week 36). Although 3 different approaches will be used, only the first approach will be used with respect to determining success. The other 2 approaches will not be considered in the multiplicity adjustment and are considered exploratory.

4. Proportion of patients who begin rescue treatment prior to and including week 36. The denominator for each group will be all patients randomized to that group. The numerator will be those who start rescue treatment prior to and including week 36.

5.1.3 *Descriptive Endpoints*

1. [redacted]

[redacted]

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5.1.4 *Exploratory Efficacy Endpoints*

1. [redacted]

[redacted]

3. [redacted]

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5.1.5 [redacted]

1. [redacted]

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5. [redacted]

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[redacted]

9. [redacted]

5.2 Safety Endpoints

1. Incidence of adverse events (AEs)
2. Incidence of adverse events of special interest (AESI) overall and by AESI.
3. Absolute and change from baseline to each study visit in blood chemistry parameters
4. Absolute and change from baseline to each study visit in blood hematology parameters
5. Absolute and change from baseline to each study visit for Vital Signs (HR, SBP, DBP, Body Weight) and 12-lead ECG (PR, QRS, QTcF, HR)
6. Incidence of clinically significant findings on abdominal ultrasound

6 Statistical Methodology

6.1 General Methodology

The following is a list of general reporting conventions:

- Percentages will be based on the number of subjects in the analysis set unless otherwise indicated.

- Categorical variables will be summarized using counts (n) and percentages (%) and will be presented in the form of n (%).
- Percentages will be reported to 1 decimal place.
- Continuous data will be summarized using the mean, standard deviation (SD), median, minimum, 25th and 75th percentiles, maximum, and number of subjects with data.
- Means and medians will be reported at 1 more significant digit than the precision of the data. Standard deviations and confidence intervals will be reported at 2 more significant digits than the precision of the data. Quartiles, minima and maxima will be reported to the same level of precision as the original observations.
- The median will be reported as the average of the 2 middle numbers if the dataset contains even numbers.
- No preliminary rounding should be performed; rounding should only occur after analysis. To round, consider digit to right of last significant digit: if < 5, then round down; if ≥ 5, then round up.
- All p-values will be reported to 3 decimal places (e.g., 0.XXX). Values < 0.001 will be reported as < 0.001.

If departures from these general conventions are present in the specific evaluations sections of this SAP, then those conventions will take precedence over these general conventions.

6.2 Visit Windows

The following table outlines the analysis visits that data will be mapped to for analysis of data collected during Screening and the DPC period. Data will be analysed using the nominal visit, except in the case of an unscheduled visit that occurs between week 34 and week 36 which is in the place of a missing week 34 visit. These visits will be mapped to the scheduled visit (i.e., week 34). All other unscheduled visits will be listed, but not mapped to a specific analysis visit.

Study Visit	**Analysis Visit**
Screening 1	Screening 1
Screening 2	Screening 2
Baseline	Baseline
Week 4	Week 4
Week 8	Week 8
Week 12	Week 12
Week 16	Week 16
Week 20	Week 20
Week 24	Week 24
Week 28	Week 28
Week 32	Week 32
Week 34	Week 34
Week 36	Week 36

The following table outlines the analysis visits data will be mapped to for analysis of data collected during the OLE period. Data will be analysed using the nominal visit. All unscheduled visits will be listed, and included in derivations, but not mapped to a specific analysis visit.

Study Visit	Analysis Visit
Baseline	Baseline
Week 4	Week 4
Week 8	Week 8
Week 12	Week 12
Week 16	Week 16
Week 20	Week 20
Week 24	Week 24
Week 36	Week 36
Week 46	Week 46
Week 48	Week 48
Week 60, 72, 84, …(i.e, every 12 weeks)	Week 60, 72, 84, …(i.e, every 12 weeks)

6.3 Missing Data, Outliers, Pooling and Multiplicity

6.3.1 *Missing Data*

As the rules for imputation of missing data will differ by endpoint, details on imputation rules for missing data are provided with the description of the endpoint and analytical methods for analysis.

6.3.2 *Outliers*

All reported values will be included in the analyses.

6.3.3 *Pooling*

Based on the total sample size of the study, and the anticipated number of sites, patients will be pooled across all sites, for all analyses.

6.3.4 *Sub Groups*

The following sub-groups will be investigated;

- Region (US sites vs. non-US sites)
- Gender
- Age
- Race

6.3.5 *Multiplicity*

As there is a single primary endpoint, with a single primary hypothesis test, no adjustment for multiplicity is needed for the primary endpoint/hypothesis test.

To adjust for multiplicity among the secondary endpoints, a fixed testing order will be used. The secondary endpoints will be tested in the pre-specified order as outlined in section 5.1.2, if the primary endpoint is found to statistically significant. Testing will proceed to the next endpoint if the preceding endpoint is found to be statistically significant at the 5% (two-sided) level. The moment and endpoint is found not to be significant at the 5% (two-sided) level, all remaining endpoints will be considered exploratory, instead of confirmatory. No adjustment for multiplicity will be made for the exploratory endpoints.

The OLE period is viewed as s sub-study. No adjustment for multiplicity for the OLE endpoints will be made.

There will be no statistical analyses of baseline characteristics, demographics or safety endpoints.

6.4 Study Sample

6.4.1 *Disposition*

A clear accounting of disposition, including the numbers and percentages of patients screened, randomized, completed the DPC period, enrolled into the OLE and completed the OLE will be reported overall and by treatment group. In addition, the primary reasons for screen failure, for early discontinuation of therapy (including those that met pre-defined withdrawal criteria) during the DPC period and early discontinuation during the OLE will be reported overall and by treatment group.

A graphical and tabular summary of the time to discontinuation during the DPC period and during the OLE will also be provided overall and by treatment group.

A summary of the number of patients included in each analysis population will be provided overall and by treatment group.

All subjects who were randomized but withdrew from the study during the DPC period and during the OLE will be provided in a listing, with the reason(s) for discontinuation.

All subjects excluded from the per-protocol set will be listed with the reason(s) for exclusion.

6.4.2 *Protocol Violations and Treatment Compliance*

For the FAS set, all major protocol violations (e.g., administration of a prohibited concomitant medication, violation of inclusion/exclusion criteria) will be listed by site, including action taken (e.g. discontinuing a subject), if any.

A tabular summary of all major protocol violations will be provided by site, and overall, by treatment group and overall. Major protocol violations will be classified as:

- Violations of inclusion and exclusion criteria
- Receiving the wrong study medication
- Non-compliance with study medication. A patient is defined as non-compliant if the patient took < 75% of the study medication.
- Taking a prohibited medication or receiving a prohibited therapy
- Other

6.5 Demographics and Baseline Summaries

Demographic and baseline characteristics will be summarized by treatment group for the FAS set and the OLE set, by treatment group and overall, using descriptive statistics. If the FAS and safety set are different, then summaries will also be presented for the safety set. No statistical hypothesis tests will be performed.

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;
- 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 be 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)
- Average IGF-1 levels (in ULN values) at Baseline (Based on the Average of the 2 assessments within 2 weeks prior to randomization)
- GH levels in mg/mL at Baseline

The following continuous baseline disease characteristics data will also be included for the OLE only:

- Average IGF-1 levels (in ULN values) at Baseline of the OLE (Based on the Average of the last 2 assessments during the DPC period)
- GH levels in mg/mL at Baseline of the OLE (Based on the last value collected during the DPC period)

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)
- Residual Tumor Size: No remnants, < 5mm, 5-10 mm, >10 mm
- Prior Injectable Treatment Octreotide LAR (low, middle and high doses) and Lanreotide (low, middle and high doses)
- Prior Injectable Treatment Overall (low, middle and high doses)
- Prior Injectable Treatment Overall (low vs. middle and high doses)

The following categorical baseline disease characteristics data will also be included for the OLE set only:

- Response in DPC (based on last 3 measures – CR, PR, NR
- Final Dose in DPC
- Met pre-defined withdrawal criteria in DPC

6.6 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 18.1 or greater and summarized by system organ class (SOC) and preferred term for each treatment group, and overall. At each level of summarization, a patient is counted once if he/she reported one or more medical history terms at that level.

6.7 Concomitant Medications/Therapies/Procedures

Concomitant medications/therapies/procedures are those that are taken/performed at any time after the first dose of study medication.

If the start day of a medication/therapy/procedure is missing, then if the month and year of the start date are on or after the date of randomization, the following rules will be applied:

- If month/year of the stat date is equal or after the month/year of the date of randomization, the medication/therapy/procedure will be considered concomitant;
- If month/year of the start date is equal to the month/year of the date of randomization, and the end date is present, the end date will be used to determine if the medication/therapy/procedure stopped prior to randomization or after. If the end date is after, the medication/therapy/procedure will be considered concomitant; otherwise, if the medication/therapy/procedure stopped prior, then it will be considered to be prior;
- If month/year of the start date is equal to the month/year of the date of randomization, and the end date is a partial date, the medication/therapy/procedure will be considered concomitant;
- If, despite implementing the above conventions, the start date of the medication/therapy/procedure cannot be placed before, on, or after randomization, then the medication/therapy/procedure will be considered concomitant.

Concomitant medications will be coded using the The World Health Organization (WHO) Drug Dictionary (September 2015 or later) and summarized by drug class (ATC Level 3) and preferred term for each treatment group. MedDRA 18.1 will be used to map each reported therapy/procedure to a specific ATC Level 4 and PT.

The summaries will present the number and percentage of patients using each medication and each therapy/procedure, by treatment group and overall. Patients may have more than one medication (or

therapy/procedure) per drug class or preferred term. At each level of summarization, a patient is counted once if he/she reported one or more medications (or therapy/procedure) at that level.

6.8 Efficacy Analyses

6.8.1 Primary Endpoint Analysis

The primary efficacy analysis will estimate the proportion of responders, based on the primary endpoint, at the end of the DPC period, within the octreotide capsules and placebo arms. An assessment of superiority will be made using an exact logistic regression model, with covariates for treatment, baseline SRL dose (low vs mid or high) and baseline IGF-1 level (< median vs ≥ median). If the two-sided p-value is < 0.05, octreotide capsules will be declared superior to placebo. The adjusted proportions, difference in proportions and associated two-sided 95% confidence intervals will be reported. In addition, the odds ratio and two-sided 95% confidence interval (CI) will be reported. The FAS will be the primary population used for this analysis, with the PP population used as a supportive analysis.

Patients who discontinue study medication during the DPC period for any reason will be classified as non-responders for the primary analysis, regardless of their IGF-1 values. [redacted]

To assess the impact of missing data on the primary endpoint, several sensitivity analyses will be conducted using multiple imputation.

[redacted]

The primary endpoint analysis results will be reported overall and by sub-groups (region, age, gender and race). The same statistical methodology applied to the primary endpoint analysis will be used for analyzing the primary endpoint by each sub-group.

Randomization, in theory, should provide balance of all baseline characteristics, between the two treatment groups. At the conclusion of the study, if there is an imbalance in any baseline characteristics felt to be clinically meaningful, the effect of this imbalance on the primary endpoint will be evaluated through inclusion of covariates for these characteristics into the primary model above. These analyses will be considered sensitivity analyses to investigate the robustness of the primary analysis.

6.8.2 Secondary Endpoint Analyses

Analyses will be presented using both the FAS and the PP analysis set.

For the analysis of the proportion of responders based on mean GH , only patients with a screening mean GH value of < 2.5 ng/mL will be included in the analysis. GH response will be defined using the mean integrated GH value, based on 5 assessments, 30 minutes apart. Patients who discontinue treatment during the DPC period for any reason will be classified as non-responders for the GH response analysis, regardless of their GH values. If a patient is missing their week 36 mean integrated GH value, this value will be imputed using the the Markov Chain Monte Carlo (MCMC) method for multiple imputation as outlined above. The adjusted proportions will be obtained from an exact logistic regression model, with covariates for treatment, baseline SRL dose (low vs mid or high) and baseline GH level (< median vs ≥ median). The adjusted proportions, difference in proportions and associated two-sided 95% confidence intervals will be reported. In addition, the odds ratio and two-sided 95% confidence interval (CI) will be reported.

The time to loss of response will be summarized using the Kaplan-Meier method, and treatment groups will be compared using a Log-Rank test. Time zero is defined as the date time of the first dose of study medication. For each time to loss of response endpoint, three different analyses will be reported, with each of the three different analyses using a different approach (as defined earlier) to account for paitents who discontinue from the study prior to meeting the definition of loss of response.

A Fisher's Exact Test will be used to compare the proportion of patients who begin rescue treatment prior to and including week 36. The denominator for each group will be all patients randomized to that group. The numerator will be those who start rescue treatment prior to and including week 36. The proportions within each treatment group, difference in proportions and exact two-sided 95% confidence interval will be reported.

After the study has completed, if there is an imbalance in any baseline characteristics felt to be clinically meaningful, the effect of this imbalance on the secondary endpoints will be evaluated through inclusion of covariates for these characteristics into the models described above. These analyses will be considered sensitivity analyses to investigate the robustness of the primary analyses for the secondary endpoints.

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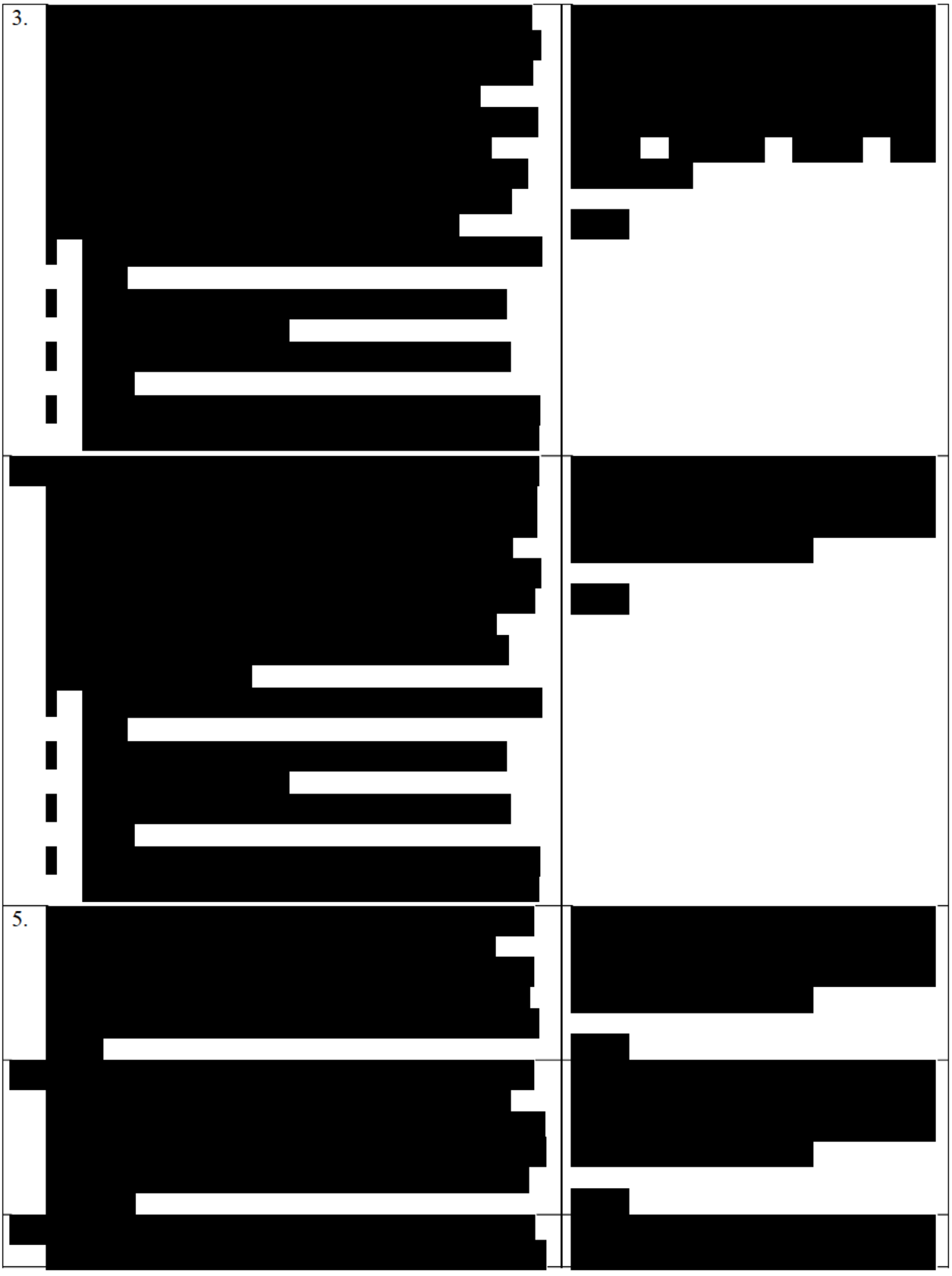
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6.9 Safety Analyses

All safety analyses for data collected during the DPC period will be presented using the safety set. All safety analyses for data collected during the OLE will be presented using the OLE set (summaries by treatment group will be based on the treatment group in the DPC period). Safety analyses for the DPC period will only use data collected during the DPC period, and will exclude any safety data that was collected after a subject had discontinued study drug. Safety analyses for the OLE will include data collected during the OLE. No formal hypothesis testing will be conducted. Data will be summarized using appropriate descriptive statistics. Missing data will be maintained as missing, unless indicated.

6.9.1 Study Drug Exposure and Compliance

6.9.1.1 DPC period

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

In the DPC period, the duration of study drug exposure (in days) will be summarized by the treatment group and overall, using descriptive statistics. Duration of study drug exposure will be calculated as date of last dose in the DPC period – date of first dose in the DPC period + 1.

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 also be presented by treatment group. 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) at the end of the DPC period, will also be presented by treatment group.

Compliance to each dose level of octreotide capsules from first dose in the DPC period through the last visit of the DPC period will be calculated and summarized by treatment group overall, and also by the final target dose level achieved within each treatment group.

For the purpose of analysis, compliance to each dose level during the DPC period 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 DPC period. The numbers and percentages of patients <75% compliant, 75-100% compliant, and >100% 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

A summary of the number of patients who re-initiated SRL treatment in the DPC period will also be provided and will show the number of patients who re-intitaited SRL treatment by time point and treatment arm.

6.9.1.2 OLE Phase

Octreotide capsules can be up-titrated or down titrated during the OLE. All patients will start on 60 mg/day and can either down titrate to 40 mg/day or up titrate to 80 mg/day, based on clinical and biochemical response.

In the OLE, the duration of study drug exposure (in days) will be summarized by the treatment group and overall, using descriptive statistics. Duration of study drug exposure will be calculated as date of last dose in the OLE– date of first dose in the OLE + 1.

The number and proportion of patients at each dose level (40, 60 and 80 mg/day) at the end of the OLE, will also be presented by treatment group and overall.

Compliance to each dose level of octreotide capsules from first dose in the OLE through the last visit of the OLE will be calculated and summarized by treatment group and overall, and also by the final target dose level achieved within each treatment group during the OLE.

For the purpose of analysis, compliance to each dose level during the OLE 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 OLE. The numbers and percentages of patients <75% compliant, 75-100% compliant, and >100% 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

6.9.2 *Adverse* E*vents*

Adverse events will be coded using MedDRA (version 18.1 or higher).

6.9.2.1 DPC period

All AEs that occur after randomization (i.e., date of onset is on or after the date of randomization) and on or before the end of treatment (last dose of blinded study drug) in the DPC period will be considered Treatment Emergent Adverse Events (TEAEs) for the purpose of reporting in the DPC period, and will be summarized using frequency counts and percentages. Summaries will be presented by final dose group and treatment group (i.e., octreotide 40, 60, 80, overall and placebo) and overall for the safety set.

If the day of onset of an AE is missing, then if the month and year of an onset date are on or after the date of randomization, the following rules will be applied:

- If month/year of the onset date is on or after the month/year of randomization, the AE will be considered treatment emergent;
- If month/year of the onset date is equal to the month/year of randomization, and the end date is present, the end date will be used to determine when the AE started. If the end date is on or after randomization, the AE will be considered treatment emergent; otherwise, if the AE stopped before randomization, then it will not be considered treatment emergent;
- If month/year of the onset date is equal to the month/year of randomization, and the end date is a partial date, the AE will be considered treatment emergent;
- If, despite implementing the above conventions, the onset date of the AE cannot be placed before, on, or after randomization, then the event will be considered treatment emergent.

Summaries of TEAEs will be presented using the MedDRA level hierarchy (system organ class, high level group term, high level term, and preferred term) as follows:

- Overall (i.e., regardless of intensity or relationship to treatment)
- By intensity grade (mild, moderate, severe)
- By relationship to study medication (potential relationship to study treatment or unlikely/no relationship to study treatment) according to the mapping scheme below:
    - Related: will include all AEs with a relationship rating of “related” or “possibly related”
    - Not related: will include all AEs with a relationship rating of “Not related”
- Unless otherwise specified, at each level of patient summarization in reporting the incidence of the AEs, a subject will be counted once if the subject reported one or more events. If more than one occurrence of an event is reported, the event of the worst intensity or the worst-case relationship assessment will be summarized.

TEAEs leading to premature discontinuation of study drug and serious TEAEs (SAEs) will also be summarized by treatment group and relationship. TEAEs leading to premature discontinuation of study drug will be defined as any TEAEs with an action taken regarding study medication equal to "permanently discontinued."

Summaries of TEAEs overall, by relationship, leading to premature discontinuation and serious TEAEs will also be presented by sub-groups (region, age, gender and race) using descriptive statistics.

Summaries of AESI will be presented by intensity grade both overall and by individual AESI. The following are the AESIs which will be reported: headache, fatigue, perspiration, soft tissue swelling, arthralgia, dysglycemia, and hypertension. Additional AEs identified by the investigator may also be included as AESIs. In addition, summaries, will also be presented for AESIs leading to premature discontinuation of study drug, by severity. Unless otherwise specified, at each level of patient summarization in reporting the incidence of the AESIs, a subject will be counted once if the subject reported one or more events. If more than one occurrence of an event is reported, the event of the worst intensity will be summarized. An overall summary of the number and propotion of patients reporting 0,1, 2, 3 and >3 AESIs will also be provided.

6.9.2.2 OLE

AEs will be considered treatment emergent for the purpose of reporting in the OLE if they meet any of the following criteria:

- AE onset date is after the end of treatment in the DPC period (i.e., date of onset greater than the end of treatment date in the DPC period)
- AE is ongoing, and the severity worsens during the OLE (i.e., date of severity worsening is greater than the end of treatment date in the DPC period)

All summaries will be presented by final dose group (i.e., 40, 60 or 80) and overall for the OLE set.

If the day of onset of an AE is missing, then if the month and year of an onset date are on or after the date of randomization, the following rules will be applied:

- If month/year of the onset date is on or after the month/year of the end of treatment date in the DPC period, the AE will be considered treatment emergent;
- If month/year of the onset date is equal to the month/year of the end of treatment date in the DPC period, and the end date is present, the end date will be used to determine when the AE started. If the end date is on or after the end of treatment date in the DPC period, the AE will be considered treatment emergent; otherwise, if the AE stopped before randomization, then it will not be considered treatment emergent;
- If month/year of the onset date is equal to the month/year of the end of treatment date in the DPC period, and the end date is a partial date, the AE will be considered treatment emergent;
- If, despite implementing the above conventions, the onset date of the AE cannot be placed before, on, or after the end of treatment date in the DPC period, then the event will be considered treatment emergent.

Summaries of TEAEs will be presented using the MedDRA level hierarchy (system organ class, high level group term, high level term, and preferred term) as follows:

Overall (i.e., regardless of intensity or relationship to treatment)

By intensity grade (mild, moderate, severe)

By relationship to study medication (potential relationship to study treatment or unlikely/no relationship to study treatment) according to the mapping scheme below:

Related: will include all AEs with a relationship rating of "related" or "possibly related"

Not related: will include all AEs with a relationship rating of "Not related"

Unless otherwise specified, at each level of patient summarization in reporting the incidence of the AEs, a subject will be counted once if the subject reported one or more events. If more than one occurrence of an event is reported, the event of the worst intensity or the worst-case relationship assessment will be summarized.

TEAEs leading to premature discontinuation of study drug and serious TEAEs (SAEs) will also be summarized by treatment group and relationship. TEAEs leading to premature discontinuation of study drug will be defined as any TEAEs with an action taken regarding study medication equal to "permanently discontinued."

6.9.3 *Laboratory Parameters*

Descriptive summary statistics for chemistry and hematology data at each post randomization time point (both absolute and change) will be presented by final dose group and treatment group (i.e., octreotide 40, 60, 80, overall and placebo). Summaries will be provided for the DPC period and for the OLE period. In calculating the change from baseline for both the DPC and for the OLE, the baseline for the DPC period will be used.

Shift tables, summarizing individual subject changes from baseline to end of treatment will be presented for each laboratory parameter, by treatment group, using the normal ranges from the central laboratory. An additionial shift anlaysis will be presented for glucose using the levels within the common terminology criteria for adverse events (CTCAE) version 4.03. Summaries will be provided for both the DPC period and OLE period. For both the DPC period and the OLE period summaries, baseline will be the baseline defined for the start of the DPC period.

Subjects with clinically significant abnormalities (based on investigator's assessment) will be identified in listings.

All tabular summaries will exclude any data that was collected after a subject had discontinued study drug. Data collected after a subject had discontinued study drug will be included in listings.

6.9.4 *Vital Signs and Body Weight*

Descriptive statistics of vital sign (systolic blood pressure, diastolic blood pressure, heart rate, body weight) data at each post randomization time point (both absolute and change) will be presented by final dose group and treatment group (i.e., octreotide 40, 60, 80, overall and placebo). Summaries will be provided for the DPC period and for the OLE period. In calculating the change from baseline for both the DPC and for the OLE, the baseline for the DPC period will be used.

Additionally, shift tables, summarizing individual subject changes from baseline to end of treatment will be presented for heart rate, diastolic and systolic blood pressure, by final dose group and treatment group (i.e., octreotide 40, 60, 80, overall and placebo), using the categories outlined in the common terminology criteria for adverse events (CTCAE) version 4.03.

These will be presented for both the DPC period and OLE period. For both the DPC period and the OLE period, shifts from baseline will use the baseline defined for the start of the DPC period.

Subjects with clinically significant abnormalities will be identified in listings.

All tabular summaries will exclude any data that was collected after a subject had discontinued study drug. Data collected after a subject had discontinued study drug will be included in listings.

6.9.5 *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 by final dose group and treatment group (i.e., octreotide 40, 60, 80, overall and placebo). Both absolute and change from baseline will be provided for each continuous 12-Lead ECG parameter. Summaries will be provided for the DPC period and for the OLE period. In calculating the change from baseline for both the DPC and for the OLE, the baseline for the DPC period will be used.

Additionally, the numbers and percentages of patients with ECG abnormalities (as determined by the central laboratory) at each visit will be presented for both the DPC and for the OLE. 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 for both the DPC and for the OLE periods. For both the DPC period and the OLE period, shifts from baseline will use the baseline defined for the start of the DPC period.

A listing of patients with clinically significant ECG abnormalities (using the high and low cut points above) will be provided in listings.

All tabular summaries will exclude any data that was collected after a subject had discontinued study drug. Data collected after a subject had discontinued study drug will be included in listings.

6.9.6 *Abdominal Ultrasound*

The following information will be summarized at baseline and end of treatment for the DPC period using shift tables, by final dose group and treatment group (i.e., octreotide 40, 60, 80, overall and placebo):

- 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)

For the OLE period, shift tables will also be provided to show shifts from baseline of the DPC period to each assessment in the OLE period.

All tabular summaries will exclude any data that was collected after a subject had discontinued study drug. Data collected after a subject had discontinued study drug will be included in listings.