NOVARTIS

Clinical Development

Pasireotide LAR / SOM230 LAR

CSOM230C1202 / NCT01673646

A multicenter, open-label, randomized, phase II study to evaluate efficacy, safety, pharmacokinetics and pharmacodynamics of pasireotide LAR in Japanese patients with active acromegaly or pituitary gigantism

RAP Module 3 – Detailed Statistical Methodology for final CSR

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Document History – Changes compared to previous version of RAP module 3.

Version	Date	Changes
1.0	13-Jul- 2016	Initial version of RAP Module 3 for final CSR
Amendment 1.0	See title page	1. Some previously reported baseline characteristic data have been changed and summary will be re-generated: • Medical history and current medication conditions in section 5.5 • Prior medication in section 5.6. 2. Section 5.10.2.1 liver function parameters are newly inserted. 3. Safety disclosure section with two tables related to adverse events (non-serious AE and death due to SAE) are added in order to comply with legal requirements pertinent to the disclosure of study results (Section 5.10.1)

1 Introduction

This document describes the detailed statistical methodology of the Report Analysis Plan (RAP) of Study SOM230C1202 required for reporting the results of final clinical study report (CSR).

The first analysis, for the purpose of the First Interpretable Results (FIR) only, was conducted when the last patient completed the Month 3 assessment with data cut-off date on 31-Jul-2014. The second analysis was conducted, when the last patient completed the Month 12 assessments (with data cut-off date on 2-Apr-2015), and the results were reported in an interim CSR dated 01-Jul-2015. Details on the final analysis are provided in the Section 4.2 for final CSR. For completeness a short description of prior analysis is provided in the same section.

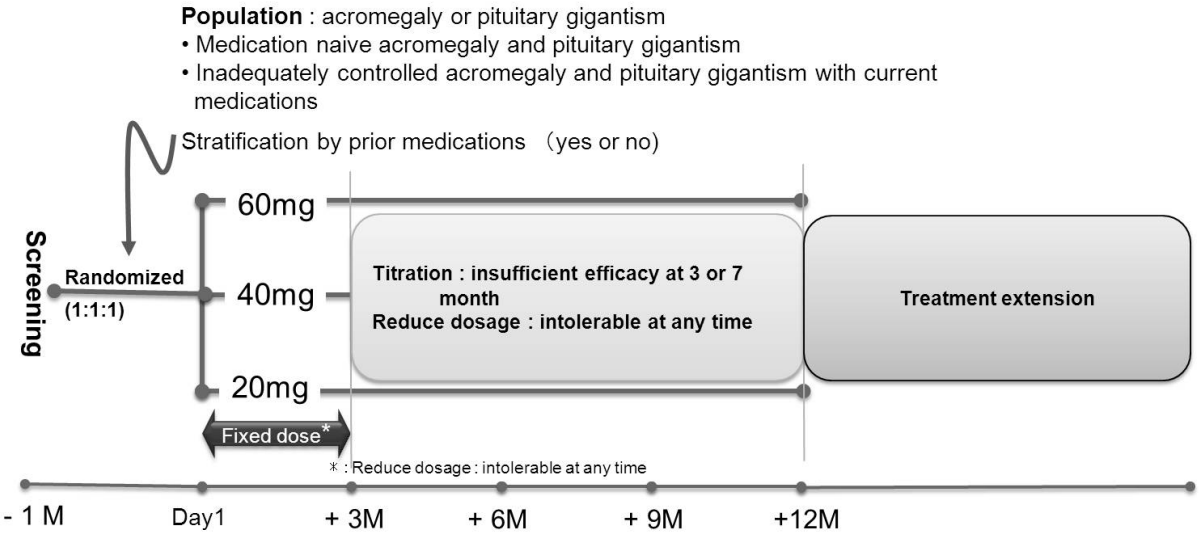
Data will be analyzed by Novartis personnel or a designated third party. This RAP contains relevant statistical considerations for the final analysis which will contain cumulative data generated from first patient first visit (FPFV) to last patient last visit (LPLV) until all patients have withdrawn study. Further supportive statistical information will be provided in the [Appendix 16.1.9 of the CSR].

2 Study design

A total of 33 eligible patients were enrolled and randomized to one of 3 doses of pasireotide LAR (20 mg, 40 mg, or 60 mg) in a ratio of 1:1:1. Randomization was stratified by prior medications (e.g. somatostatin analogues or dopamine agonists), (yes or no). Intramuscular administration of pasireotide LAR has been repeated every month (1 month = 28 days) for 12 months in core phase. It is permitted to increase the dose up to 60 mg in a patient showing the following biochemical test results after 3 and 6 months of study treatment: mean GH levels ≥2.5 µg/L and/or IGF-1 > ULN (age and sex related). In the event of any problem with tolerability, it is permitted to reduce the next lower dosage level at any time. After 3 months of study treatment, the primary endpoint (proportion of patients with a reduction of mean GH levels to <2.5 µg/L and normalization of IGF-1 to within normal limits) will be evaluated.

Patients with a reduction of mean GH levels to <2.5 µg/L and normalization of IGF-1 at the end of the 12-month study treatment will be enrolled in an extension phase of study treatment. Patients with a mean GH level ≥ 2.5 µg/L and/or IGF-1 > ULN at the end of the 12- month study treatment may be enrolled in an extension phase of study treatment if the extended study treatment is thought to be clinically beneficial for them by the investigator. Patients will receive pasireotide LAR in the extension phase until unacceptable toxicity appears or until the medication is commercially available or until the pasireotide LAR development program is discontinued whichever comes first.

Figure 2-1 Study design



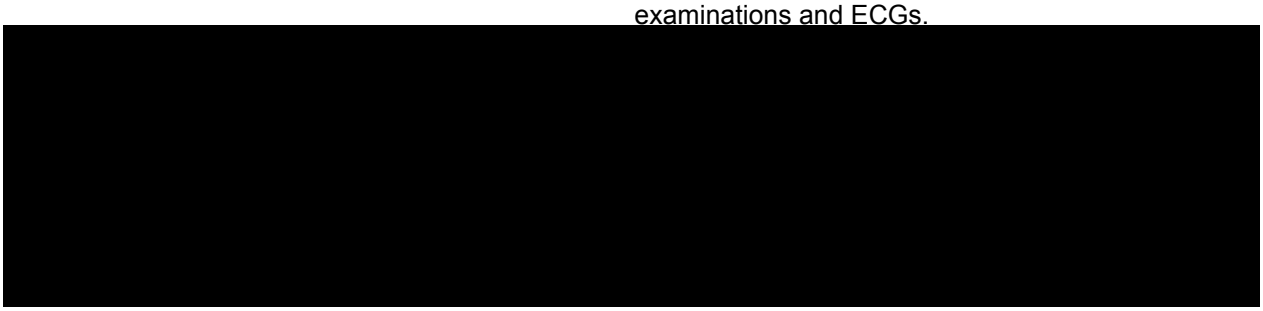
3 Objectives

Table 3-1 Objectives and related endpoints

Objective	Endpoint
Primary	
Assess the total-group efficacy of pasireotide LAR on the reduction of mean GH levels to < 2.5 µg/L and the normalization of IGF-1 at 3 months of study treatment	Proportion of patients with a reduction of mean GH levels to < 2.5 µg/L and the normalization of IGF-1 to within normal limits (age and sex related) at 3 months across all doses
Key secondary	
Assess the effect of each starting dose pasireotide LAR on the reduction of mean GH levels to < 2.5 µg/L and the normalization of IGF-1 at 3 months of study treatment	Proportion of patients with a reduction of mean GH levels to < 2.5 µg/L and the normalization of IGF-1 to within normal limits (age and sex related) at 3 months in each starting dose
Assess the PK and PK/PD of pasireotide LAR 20 mg, 40 mg and 60 mg	PK: C_{trough}, $C_{max,\ 3rd\ inj}$, accumulation ratio (AR) PD: GH, IGF-1
Assess the tolerability and safety profile of pasireotide LAR at 3 months and during and after the 12- month study treatment	Toxicity will be assessed using the National Cancer Institute-Common Toxicology Criteria (NCI-CTC) grading scale for Adverse Events and for laboratory assessments that include biochemistry and hematology; special safety assessments that include the regular monitoring and recording of blood glucose, HbA1c, thyroid and liver function tests, gallbladder examinations and ECGs.
Assess the effect of pasireotide LAR on the reduction of mean GH levels to < 2.5 µg/L at 3 months of study treatment	Proportion of patients with a reduction of mean GH levels to < 2.5 µg/L at 3 months

Objective	**Endpoint**
Assess the effect of pasireotide LAR on the normalization of IGF-1 at 3 months of study treatment	Proportion of patients with the normalization of IGF-1 to within normal limits (age and sex related) at 3 months
Other secondary (Core phase)	
Assess the effect of pasireotide LAR on the reduction of mean GH levels to < 2.5 µg/L and the normalization of IGF-1 at 6, 9 and 12 months of study treatment	Proportion of patients with a reduction of mean GH levels to < 2.5 µg/L and the normalization of IGF-1 to within normal limits (age and sex related) at 6, 9 and 12 months
Assess the effect of pasireotide LAR on the reduction of mean GH levels to < 2.5 µg/L at 6, 9and 12 months of study treatment	Proportion of patients with a reduction of mean GH levels to < 2.5 µg/L at 6, 9 and 12 months
Assess the effect of pasireotide LAR on the normalization of IGF-1 at 6, 9 and 12 months of study treatment	Proportion of patients with the normalization of IGF-1 to within normal limits (age and sex related) at 6, 9 and 12 months
Assess the effect of pasireotide LAR on the change of tumor volume at 6and 12 months of study treatment	Change of tumor volume from baseline at 6 and 12 months
Assess the effect of pasireotide LAR on the change of mean GH level from baseline	Change of mean GH levels from baseline
Assess the effect of pasireotide LAR on the symptoms of acromegaly, specifically: ring size, headache, fatigue, perspiration, paresthesias, osteoarthralgia	Change of clinical signs from baseline: ring size, headache, fatigue, perspiration, paresthesias, osteoarthralgia
Assess the effect of pasireotide LAR on the change of prolactin (PRL) level from baseline	Change PRL level from baseline
Other secondary (Extension phase)	
Assess the effect of pasireotide LAR as long term study treatment on the proportion of patients with a reduction of mean GH level to < 2.5 µg/L and normalization of IGF-1 at 18 and 24 months of study treatment	Proportion of patients with a reduction of mean GH levels to < 2.5 µg/L and the normalization of IGF-1 to within normal limits (age and sex related) a18 and 24 months of study treatment
Assess the effect of pasireotide LAR as long term study treatment on the reduction of mean GH levels to < 2.5 µg/L at 18 and 24 months of study treatment	Proportion of patients with a reduction of mean GH levels to < 2.5µg/L at 18 and 24 months of study treatment
Assess the effect of pasireotide LAR as long term study treatment on the normalization of IGF-1 at 18 and 24 months of study treatment	Proportion of patients with the normalization of IGF-1 to within normal limits (age and sex related) at 18 and 24 months of study treatment
Assess the effect of pasireotide LAR as long term study treatment on the change of mean GH levels from baseline	Change of mean GH levels from baseline in extension phase
Assess the safety and tolerability of pasireotide LAR in extension phase	Toxicity in extension phase will be assessed using the National Cancer Institute-Common Toxicology Criteria (NCI-CTC) grading scale for Adverse Events
Assess the total-group safety and tolerability of pasireotide LAR as long term study treatment	Toxicity in total-group study treatment will be assessed using the National Cancer Institute-Common Toxicology Criteria (NCI-CTC) grading

Objective	Endpoint
	scale for Adverse Events and for laboratory assessments that include biochemistry, hematology, urinalysis; special safety assessments that include the regular monitoring and recording of blood glucose, HbA1c, thyroid and liver function tests, gallbladder examinations and ECGs.



4 Definitions and general methodology

4.1 Definitions

4.1.1 Study drug and study treatment

Study drug will refer to SOM230 (pasireotide) LAR.

4.1.2 Date of first administration of study drug

The date of first administration of study drug will be derived as the first date when a nonzero dose of study drug is administered and recorded on the dose administration record (DAR) page of the electronic case report form (eCRF). For the sake of simplicity, the date of first administration of study drug will also be referred as start date of study drug.

4.1.3 Date of last administration of study drug

The date of last administration of study drug will be defined as the last date when a nonzero dose of study drug is administered and recorded on DAR page of the eCRF. This date will also be referred as last date of study drug.

4.1.4 Study day

The study day for all assessments (i.e. efficacy, safety) will be calculated as the difference between the date of the event (i.e. visit date, onset date of an event, assessment date) and the first date of study drug plus 1. For patients who got randomized but never dosed, study day is calculated as the difference between the date of event and the date of randomization plus 1.

For any assessment or event such as baseline disease characteristics or medical history that is supposed to occur prior to the start of study drug, the study day will be negative and calculated as the difference between the date of the event and the first date of study drug.

The study day will be displayed in the data listings.

4.1.5 Baseline

The baseline will be the last pre-treatment evaluation result within 28 days of the start date of study drug.

4.1.6 On-treatment assessment/event

Safety summaries and selected summaries of deaths will be presented using only on-treatment assessments/events.

For patients who discontinue study drug, on-treatment assessment/event will be any assessment/event obtained in the time interval between start date of study drug and last date of study drug + 56 days.

4.1.7 Month

A month will be calculated as 28 days. If duration in months has to be reported, duration in days will be divided by 28.

4.1.8 Standardized IGF-1

IGF-1 normal range is age and gender dependent. When pooling all the data for analyses, unless otherwise specified, the standardized IGF-1 will be used. The standardized IGF-1 is defined as:

$$\text{Standardized IGF-1} = \text{IGF-1 value} / \text{ULN},$$

where ULN is the upper limit of the normal range.

4.1.9 Handling of missing values/censoring/discontinuations

If the GH and/or IGF-1 samples are taken after 35 days (=28 + 7 days) from the date of LAR injection, the values if GH and/or IGF-1 at the corresponding visit will be treated as missing. In addition, if a patient has less than 3 samples for the assessment of 5-point mean GH levels from the 2-hour profile, the mean GH levels will be considered as missing.

The patients with missing values of mean GH levels and/or IGF-1 at 3 months of study treatment or who discontinue prior to the assessment at 3 months of study treatment will be considered as non-responders.

4.1.10 Evaluation time window

GH and IGF-1 measurements taken within 35 days after the date of LAR injection are allowed and the last values of 5-point mean GH and IGF-1 within window will be used as the value of the corresponding month. For assessments beyond 3 months of study treatment, the ongoing patients will be counted in the denominator of calculation of response rate, if they have reached at each visit (e.g. Assessments collected at end of the study treatment of Core Phase will be treated at those at 12 months of study treatment as long as those were collected within the time window specified in the above). Discontinued patients are included in the denominator of calculation of response rate in the core phase and are included at a visit to which a patient reached in the extension phase.

MRI collected within +/- 35 days from the date of visit is allowed. For corresponding visit, the patient will be counted at a specific visit if they have reached at each visit.

4.2 Data included in the analyses

The first interpretable result (FIR) was generated when the last patient completed 3 months assessment with data cut-off on 31-Jul-2014. Primary CSR, which contained results of primary and key secondary analyses, was generated when the last patient completed the 12 months assessment with data cut-off on 2-Apr-2015.

The final analysis will be performed after all patients discontinued the study or study drug has been available on the market, and cumulative data will be reported in a final CSR. For the final analysis, only data through 24 months of study treatment and data at end of study treatment visit will be summarized, except for study disposition and adverse events/serious adverse events, as only minimal data will be collected beyond 24 months of study treatment. Study disposition and adverse events/serious adverse events data beyond 24 months will be summarized in addition to listings.

For efficacy endpoints, all primary and key secondary analyses were already reported in 12 month CSR. Updates of other secondary endpoints will be provided in the final CSR.

If an event continues until the end, then the event will be considered continuing and not having documented end date. This approach applies, in particular, to adverse event and concomitant medication reports. For these events, the end date will not be imputed and therefore will not appear in the listings.

If it is required to impute an end date to be able to perform a specific analysis, (e.g. end date after the cut-off date) the data cut-off date will be imputed as the end date (to allow for calculation of treatment exposure duration for instance).

4.3 Analysis sets

Full analysis set (FAS) comprises of all patients to whom study treatment has been assigned by randomization. According to the intent to treat principle, patients will be analyzed according to the study treatment they have been assigned to during the randomization procedure.

Safety set includes all patients who received at least one dose of study treatment. Patients will be analyzed according to the study treatment according to the treatment they first received.

The rules for patient classification in the analysis sets (FAS and safety) are described hereafter:

Table 4-1 Patient classification rule

Analysis set	Protocol deviations that cause patients to be excluded from analysis and corresponding deviation codes from VAP Module 3
FAS	No written informed consent prior to any procedure (deviation code = I01)
Safety set	No written informed consent prior to any procedure (deviation code = I01)

The per-protocol set (PPS) and pharmacokinetic analysis set (PAS) discussed on the study protocol, will not be used for the final analysis since there is no pharmacokinetic analysis nor PPS analysis performed and all of them were already reported in [the 12 month CSR].

Although there is no PPS involved, all protocol deviations will be finalized before database lock and reported in the listing.

Analyses of efficacy endpoints will be based on the FAS. Safety analyses will be performed based on the safety set.

5 Statistical methods used in reporting

5.1 General presentation of descriptive summaries

Categorical data (e.g. gender, race, etc.) will be summarized by frequency count and percentages. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator.

Continuous data (e.g. age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum and maximum).

Data through 24 months of study treatment and at end of study treatment will be summarized except for study disposition, drug administration record and adverse events/serious adverse events. For study disposition, drug administration record and adverse events/serious adverse events, all data even beyond 24 months of study treatment will be summarized and listed.

All data will be listed appropriately.

5.2 Protocol deviation summaries

The number and percentage of patients in the FAS with any protocol deviation will be tabulated by the deviation category (as specified in the VAP Module 3).

5.3 Patient disposition

The FAS will be used for the following analyses.

Number of patients who are randomized and treated will be presented.

Number of patients who are still on-treatment, complete and discontinue at core phase will be presented. Primary reason for discontinuation at core phase will be summarized.

Number of patients who are still on-treatment, complete and discontinue at extension phase will be presented. Primary reason for discontinuation at extension phase will be summarized.

Number of patients who are beyond 24 months of study treatment and discontinue will be presented. Primary reason for discontinuation at extension phase will be summarized.

5.4 Demographics

Summary of demographics characteristics were reported in [the 12 months CSR] and not applicable in this document.

5.5 Medical history and current medical conditions

Due to few data changes since data cut-off for the analysis of [the 12months CSR], relevant medical history and current medical conditions will be summarized again by primary system organ class, preferred term, randomized dose level and overall for the FAS, although these were reported previously in [the 12 months CSR].

5.6 Prior therapies

Summaries of prior radiotherapy and surgery were reported in [the 12 months CSR] and not applicable in this document.

Due to few data changes since data cut-off for the analysis of [the 12months CSR], prior medication will be summarized again by WHO drug reference list, randomized dose level and overall for the FAS, although these were reported previously in [the 12 months CSR].

5.7 Study medication

The following analyses will be conducted by study phase for the safety set.

The durations of exposure to the study drug and the number of injections received will be summarized. Duration of exposure is calculated as

Duration of exposure = min (last date of study drug + 27, date of death) – first date of study drug + 1

Number of patients with dose reduction and dose increase will be presented.

5.8 Concomitant therapy

Concomitant medications and significant non-drug therapies prior to and after the start of the study drug will be summarized by ATC class, preferred term, phase and overall for the safety set.

5.9 Efficacy evaluation

5.9.1 Primary analysis

Primary variable

The primary variable is the total-group response rate defined as the proportion of patients with the reduction of mean GH levels to < 2.5 µg/L and the normalization of IGF-1 at 3 months of study treatment. This has already been reported in [the 12 month CSR].

Please see the Section 4.1.9 about how to handle missing values and discontinuations.

Primary analysis

The total-group response rate at 3 months of study treatment along with the corresponding Clopper-Pearson exact two-sided 90% confidence interval was reported in [the 12 months CSR]and not applicable in this document.

5.9.2 Secondary analyses

The FAS will be used for the following analyses.

5.9.2.1 Key secondary analyses

The response rate for patients with the reduction of mean GH levels to < 2.5 µg/L and the normalization of IGF-1 at 3 months of study treatment along with the corresponding exact 95% confidence interval as well as respective response rate with mean GH and IGF-1 were reported in [the 12 months CSR]and not applicable in this document.

5.9.2.2 Other secondary analyses

Other secondary analyses for core phase

Most secondary objectives were reported in [the 12 months CSR] and not applicable in this document. The below analyses, which were previously performed, will be repeated with updated data for the final analysis (most likely at 18 months and 24 months of study treatment).

Proportions of overall patients with the reduction of mean GH levels to < 2.5 ug/L and normalization of IGF-1 will be updated along with subgroup analysis of SSA uncontrolled status, while SSA uncontrolled population is defined as patients who were pre-treated with SSA for >= 12 weeks and patients who were pre-treated with SSA for < 12 weeks or were not pre-treated with SSA are considered as others. Proportions of patients with the reduction of mean GH level to < 2.5 ug/L by visit and with normalization of IGF-1 by visit will be updated along with subgroup analysis of SSA uncontrolled status, respectively.

Bar charts for all total group response rate, proportion of patients with reduction of mean GH level to < 2.5 ug/L and proportion of patients with normalization of IGF-1 will be repeated by visit for updated data.

Total group response rate with over responder by visit will be also updated where over responder is defined as a patient with reduction of mean GH levels to <2.5 ug/L and IGF-1 reached lower than lower limit normal. This summary will be updated with SSA uncontrolled status subgroups as well.

Changes from baseline in mean GH and in normalization of IGF-1 will be updated by visit and SSA uncontrolled status, respectively, in addition to change from baseline in ring size and PRL.

Plots of individual patient absolute value of mean GH and IGF-1 will be re-ran as well.

Changes of tumor volume at 6 and 12 months of study treatment from baseline were reported in [the 12 month CSR] and not applicable in this document. The summary will be repeated by subgroup of categorical longest diameter with 10 mm cut-off in the final analysis. Changes and percent changes will be plotted along with the longest diameter as well.

5.10 Safety evaluation

For all safety analyses, the safety set will be used. All analysis through Month 3 was reported in [the 12 month CSR] and not applicable in this document.

The overall observation period will be divided into three mutually exclusive segments:

1. Pre-study treatment period: from day of patient's informed consent to the day before the first dose of study medication
2. On-study treatment period: from the day of first dose of study medication to 56 days after last dose of study medication
3. Post-study treatment period: starting at 57 days after last dose of study medication

5.10.1 Adverse events (AEs)

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The last version at the time of database lock will be used.

AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. If CTCAE grading does not exist for an adverse event, grades 1-4 corresponding to the severity of mild, moderate, severe, and life-threatening will be used. CTCAE grade 5 (death) will not be used in this study; rather this information will be collected on the "Study phase completion – core study", "Study phase completion – extension study" or "Study completion" eCRF pages.

Summary tables for AEs have to include only AEs that started or worsened during the on-study treatment period, the study treatment-emergent AEs. However, all AE data (including those from the pre and post-study treatment periods) will be listed and those collected during the pre and post-study treatment are to be flagged. Serious AEs, AEs leading to study drug discontinuation, AEs requiring dose adjustment or interruption and death will be listed.

Grouping of adverse events of special interest

Specific groupings of adverse events of special interest will be considered and the number of patients with at least one event in each grouping will be reported. Such groups consist of adverse events for which there is a specific clinical interest in connection with SOM230 treatment (i.e. where SOM230 may influence a common mechanism of action responsible for triggering them) or adverse events which are similar in nature (although not identical) within project defined group. The specific groupings of AEs as defined in the latest documentation available prior to database lock [redacted] will be used.

AE summaries using all available data

The following AE summaries will be provided by phase (core/extension) using all data up to data cut-off:

- AEs, regardless of study drug relationship, by primary system organ class and preferred term
- AEs, regardless of study drug relationship, by preferred term
- AEs suspected to be related to the study drug by primary system organ class and preferred term
- AEs, regardless of study drug relationship, by primary system organ class, preferred term and maximum CTCAE grade
- AEs suspected to be related to the study drug by primary system organ class, preferred term and maximum CTCAE grade
- On-treatment deaths by primary system organ class and preferred term
- Serious AEs (SAEs), regardless of study drug relationship, by primary system organ class, preferred term and maximum CTCAE grade
- AEs leading to study discontinuation, regardless of study drug relationship, by primary system organ class, preferred term and CTCAE grade
- AEs requiring dose adjustment or study drug interruption, regardless of study drug relationship, by primary system organ class, preferred term and maximum CTCAE grade
- AEs requiring significant additional therapy, regardless of study drug relationship, by primary system organ class, preferred term and maximum CTCAE grade
- AEs of special interest, regardless of study drug relationship, by category and preferred term
- AEs of special interest suspected to be related to the study drug by category and preferred term
- AEs of special interest leading to study discontinuation, regardless of study drug relationship, by category and preferred term

Study disclosure

For the legal requirements of ClinicalTrials.gov, two required tables on on-treatment adverse events which are not serious adverse events and on on-treatment serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

5.10.2 Laboratory data

For laboratory test covered by the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, the study's biometrics and statistical reporting team will grade laboratory data accordingly. Grade 5 will not be used.

In cases differentials count, the lower limits of normal ranges used in CTCAE definition have to be replaced by a clinical meaningful limit expressed in absolute counts.

For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

Patients with laboratory abnormalities of CTC grade 3 or 4 will be listed. All laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges will be listed.

For analyses performed by core baseline diabetic status, the core diabetic status is defined as follow:

- Diabetic: patients taking any antidiabetic medication, or with history of diabetic medication or HbA1c≥6.5% or FPG ≥126 mg/dL
- Pre-diabetic: patients not qualifying as diabetic and with FPG≥100 mg/dL and < 126 mg/dL or HbA1c≥5.7% and <6.5%
- Normal glucose tolerance: patients not qualifying as diabetic or pre-diabetic and with FPG< 100 mg/dL and/ or HbA1c<5.7%.

Listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

Laboratory summaries using all available data

The following summaries using all available data will be generated by phase (core/extension):

- For hematology, biochemistry and urinary laboratory tests where CTCAE grades are defined, shift tables using CTCAE grades to compare baseline to the worst post-baseline value
- For hematology, biochemistry and urinary laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/high and low/missing classification to compare baseline to the worst post-baseline value
- For fasting serum cortisol and plasma ACTH, shift tables using the low/normal/high/high and low/missing classification to compare baseline to the worst post-baseline value will be generated.
- For fasting blood glucose and HbA1c, shift tables using the ADA (2010) to compare baseline to the last available value

- For fasting blood glucose and HbA1c, shift tables using the ADA (2010) to compare baseline to the last available value by baseline diabetic status
- For fasting blood glucose and HbA1c, summary of change from baseline over time
- For fasting blood glucose and HbA1c, summary of changes at the last value from baseline by baseline diabetic status

5.10.2.1 Liver function parameters

Liver function parameters of interest are total bilirubin (TBIL), ALT, AST and alkaline phosphates (ALP). The number (%) of subjects with worst post-baseline values will be summarized:

- ALT or AST > 3xULN
- ALT or AST > 5xULN
- ALT or AST > 8xULN
- ALT or AST > 10xULN
- ALT or AST > 20xULN
- TBL > 2xULN
- TBL > 3xULN
- ALT or AST > 3xULN & TBL >2xULN
- ALT or AST > 3xULN & TBL >2xULN & ALP < 2xULN

Potential Hy's Law events are defined as those subjects with concurrent occurrence of AST or ALT > 3xULN and TBL > 2xULN and ALP < 2xULN in the same assessment sample during the on-treatment period. Further medical review has to be conducted to assess potential confounding factor such as, liver metastases, liver function at baseline etc.

For more details and adaptation of above summary, please refer to the Oncology Hepatic Safety guidance.

5.10.3 ECG

A newly occurring ECG abnormality is defined as notable ECG abnormality at post-baseline but not at baseline. Clinically notable ECG abnormality is defined in Table 5-1. The percentage is calculated based on patients with both baseline and post-baseline evaluations. A patient with multiple occurrences of a newly occurring abnormality is counted only once for each abnormality.

The patients with newly occurring ECG abnormalities will be listed and the corresponding values will be flagged in the listing.

ECG summaries using all available data

The following summaries using all available data will be generated by phase (core/extension):

- For QTcF, QTcB and QT, shift tables to compare baseline to the worst post-baseline value
- The number of patients and percentage of patients with newly occurring ECG changes

Table 5-1 Clinically notable ECG abnormalities

ECG value	Notable ECG abnormality
QT, QTcB, QTcF [ms]	New > 450
	New > 480
	New > 500
	Increase from baseline > 30
	Increase from baseline > 60
PR [ms]	Increase from baseline > 25% and > 200
QRS [ms]	Increase from baseline > 25% and > 110
HR [bpm]	Decrease from baseline > 25% and < 50
	Increase from baseline > 25% and > 100

5.10.4 Vital signs

Patients with clinically notable vital sign abnormalities will be listed and the corresponding values will be flagged in the listing.

Vital signs summaries using all available data

- For systolic BP, diastolic BP and pulse rate, shift tables using the high/normal/low/(high and low) classification defined in Table 5-2 will be produced to compare baseline to the worst post-baseline value by phase (core/extension).

Table 5-2 Clinically notable vital signs

Vital sign	High	Low
Systolic BP [mmHg]	≥ 160 with increase from baseline of ≥ 20	≤ 90 with decrease from baseline of ≥ 20
Diastolic BP [mmHg]	≥ 100 with increase from baseline of ≥ 15	≤ 50 with decrease from baseline of ≥ 15
Pulse rate [bpm]	≥ 120 with increase from baseline of ≥ 15	≤ 50 with decrease from baseline of ≥ 15

5.10.5 Gallbladder ultrasound

Gallbladder data at each visit will be listed.

5.11 Pharmacokinetics evaluation

Pharmacokinetic data were reported in [the 12 month CSR] and not applicable in the final analysis.

[redacted]

[redacted]

6 Interim analysis

No interim analysis was planned for this study which required considerations on multiplicity. However there are multiple analyses were performed with updated data. Please see Section 4.2 for further details.

7 Sample size calculation

The planned sample size of 30 was determined based on the accuracy of estimated total-group response rate at the end of 3 months of treatment.

The response rate is the proportion of responders, where responders are defined as patients with the reduction of mean GH levels to < 2.5 µg/L and normalization of IGF-1. The response rates at 20 mg, 40mg and 60mg in Study SOM230C2110 were comparable (30% at 20mg, 41.7% at 40mg, and 38.5% at 60mg). Furthermore, the dose of pasireotide LAR will be adjusted according to efficacy and safety. It is considered, therefore, that the efficacy of pasireotide LAR can be evaluated more appropriately based on the response rate of all groups combined. In this study, based on the results from Study SOM230C2110, the expected total-group response rate will be at least 30%.

In Study SOM230C2305, patients inadequately controlled with 12 month octreotide LAR study treatment were crossed over to pasireotide LAR. The response rate at 3 months after crossover was 17.3% (two-sided 95% CI: [9.8%, 27.3%]). Since a large number of patients who enroll to this study are assumed to be inadequately controlled with octreotide LAR treatment, a clinically meaningful minimum response rate is set as 10% based on the lower limit of two-sided 95% CI, 9.8%.

The expected drop out rate is 10% based on the results from Study SOM230C2305. The patients with missing values of mean GH levels or IGF-1 at the assessment at 3 months of study treatment or who discontinue prior to the assessment at 3 months of study treatment will be considered as non-responders.

Under these assumptions, the expected total-group response rate adjusted by the expected drop out rate is 27%. The sample size of 30 can demonstrate that the lower limit of the Clopper-Pearson exact two-sided 90% CI for the total-group response rate is not less than the clinically meaningful response rate, 10%.

8 Changes from planned analysis in the protocol and Month 12 CSR

Comparing with the analysis for 12 months of study treatment CSR, the following analyses was added for final analysis (Table 8-1).

Table 8-1 List of changes from planned analysis

No.	Items	When	Note
1	Disposition table including patients who continue treatment beyond 24 months.	RAP for final CSR (See title page)	New
2	Concomitant medication by phase	RAP for final CSR (See title page)	New
3	Tumor volume by categorical longest diameter	RAP for final CSR (See title page)	New
4	Tumor volume listing with longest/shortest diameters	RAP for final CSR (See title page)	New