NOVARTIS

Clinical Development

SOM230/pasireotide

CSOM230C2413 / NCT02354508

A phase IIIb multicenter, open-label, single arm study to evaluate the efficacy and safety of pasireotide in patients with acromegaly inadequately controlled with first generation somatostatin analogues

RAP Module 3: Detailed Statistical Methodology

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

Version	Date	Changes
1.0	11-May-2015	First draft version
1.1	18-June-2015	Updated based on feedback received from LS, GBMD
1.2	26-June-2015	Updated based on feedback from Medical Writer and Trial Programmer
1.3	30-June-2015	Updated after RAP I meeting
Final 1.0	30-June-2015	Final
Amendment 1	21-March-2018	• Addition of the supportive text into the AE section related to the tables now mandatory in CSRs in order to address all current Health Authority clinical trial safety data disclosure requirements (EudraCT and CT.gov). • To add the definition of the calculation of cumulative dose and dose intensity • To specify the details on the management of the Q2 serum creatinine issue • To specify the details on the EQ-5D-5L index scores calculation • To align the definition of baseline with the safety guidance baseline definition. • Section 4.3: to change the Clinically notable values (above and below normal values) for pulse rate • Study drug start date for the extension phase was clarified. • Notable criteria for PR, QRS and VR were included.

Table of contents

List of tables

List of abbreviations

AcroQOL	Acromegaly Quality of Life
ACTH	Adrenocorticotropic Hormone
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
APTT	Activated Partial Thromboplastin Time
AST	Aspartate transaminase
ATC	Anatomic Therapeutic Chemical
ATG	Autogel
CRF	Case Report/Record form
CSR	Clinical Study Report
FBG	Fasting Blood Glucose
DAR	Dose Administration Record
DBL	Database Lock
ECG	Electrocardiogram
EQ-5D-5L	European Quality of Life group-5 dimension-5 level
GGT	Gamma-glutamyl transferase
oGTT	Oral Glucose Tolerance Test
MedDRA	Medical Dictionary for Drug Regulatory Activities
AIP	Aryl Hydrocarbon Receptor Interacting Protein
TdP	Torsades de pointes
EMA	European Medicines Agency
ADA	American Diabetes Association
GH	Growth Hormone
GPS	Global Programming and Statistical Environment
Hb	Hemoglobin
LFT	Liver Function Tests
PT(INR)	Prothrombin time (International normalized ratio)
ELISA	Enzyme-linked immunosorbent assay
HIV	Human Immunodeficiency Virus
IGF-1	Insulin-like Growth Factor 1
LAR	Long Acting Release
LPLV	Last Patient Last Visit
PLT	Platelets
PRO	Patient-reported outcome
MRI	Magnetic Resonance Imaging
PT	Preferred term
RECIST	Response evaluation criteria in solid tumors
HRQoL	Health Related Quality of Life
HbA1C	Hemoglobin A1c
PT	Prothrombin time
RAP	Report Analysis Plan
SAE	Serious Adverse Event

SOC	System organ class
VAP	Validation Analysis Plan
VAS	Visual Analogue Scale
WBC	White blood cells
WHO	World Health Organization

1 Introduction to RAP documentation

1.1 Scope

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial **CSOM230C2413.**

Module 3 (M3) provides the description of the statistical methodology used to analyze the data, **Module 7** (M7) details the presentation of the data, including shells of summary tables, figures and listings, and **Module 8 (**M8) contains programming specifications e.g. for derived variables and derived datasets, to support the creation of CSR outputs.

The statistical analysis of this study will be performed by Novartis personnel. A detailed description of the statistical analysis methods will be provided in Appendix 16.1.9 of the CSR.

Analysis data sets and statistical outputs will be produced using the most recent SAS® Version (SAS Institute Inc., Cary, NC, USA), and stored in Novartis global programming & statistical environment (GPS).

1.2 Changes to RAP documentation (M3)

Refer to corresponding guidance and NIBR RAP Addendum template for detailed information on the requirements of documenting changes to RAP documentation.

For the statistical methodology (M3), any major changes to the statistical methodology should be reflected in the RAP M3 documentation via version control (M3 amendment) (new document version to be approved by the trial team as the original module).

Such major changes could include (but are not limited to):

- change in statistical methodology
- substantial change in (derivation of) main endpoint
- substantial change in study design (e.g. protocol amendment introducing new multiple-dose cohorts in a so far single-dose trial)

Such changes may also require a protocol amendment to ensure consistency. In addition they need to be mentioned (high-level) in the CSR (section for changes to planned analysis).

Minor changes to the RAP M3 documentation can be captured e.g. by a study note to file / note in RAP Addendum or within the CSR itself. [redacted] Corrections of typographical errors or modification of spelling (from English to American, for example) do not need to be incorporated into the RAP M3 documentation.

Analyses and outputs related to [redacted] ad-hoc requests used for reporting are regarded minor changes and should be documented in the RAP addendum (no RAP amendment necessary).

2 Study objectives and design

2.1 Study reference documentation

The following documents were used to develop this RAP Module 3:

- CSR template
- Protocol CSOM230C2413
- Protocol CSOM230C2402
- Annotated Case Report Form
- Guidelines for content of Statistical Appendices of the Clinical Study Report
- Report & Analysis Plan for Novartis Oncology

2.2 Study objectives

Table 2-1 Objectives and related end points

Objective	End point
Primary	
To evaluate the efficacy of pasireotide LAR in patients with acromegaly who are inadequately controlled with maximal approved doses of currently available somatostatin analogues, as measured by the proportion of patients with GH < 1µg/L and IGF-1 <ULN at week 36	Proportion of patients who achieved GH <1µg/L and IGF-1 <ULN at week 36.
Supporting Analysis for Primary	
To assess the proportion of patients achieving GH < 1µg/L and IGF-1 <ULN at week 36 by GH level at screening.	Proportion of patients who achieved GH <1µg/L and IGF-1 <ULN at week 36 in patients having GH level at screening between 1 µg/L and 2.5 µg/L, and in patients having GH level at screening >2.5 µg/L
Secondary- core phase	
To assess the changes in mean GH from study baseline to week 36	Changes in mean GH from study baseline to week 36.
To assess the changes in standardized IGF-1 from study baseline to week 36	Changes in standardized IGF-1 from study baseline to week 36.
To assess the proportion of patients achieving GH <1 µg/L and IGF-1 <ULN at weeks 12 and 24 overall and by GH level at screening	Proportion of patients who achieved GH <1µg/L and IGF-1 <ULN at week 12 and 24 overall and by GH level at screening.
To assess the proportion of patients achieving GH <1µg/L at weeks 12, 24 and 36, overall and by GH level at screening	Proportion of patients who achieved GH <1µg/L at week 12, 24 and 36 overall and by GH level at screening.
To assess the proportion of patients achieving IGF-1 levels <ULN at weeks 12, 24 and 36	Proportion of patients who achieved IGF-1 <ULN at week 12, 24 and 36.
To evaluate the tolerability and safety profile of pasireotide LAR	Toxicity will be assessed using the National Cancer Institute-Common Toxicology Criteria Adverse Events version 4 (NCI-CTCAE v.4.03) and for laboratory

	assessments that include biochemistry, hematology, urinalysis; special safety assessments that include the regular monitoring and recording of blood glucose, insulin, HbA1c, GH and IGF-1, thyroid and liver function tests, gallbladder examinations and ECGs. Concomitant medications/Significant nondrug therapies will be assessed from study enrollment until the safety follow-up
To evaluate the effect of pasireotide LAR on HRQoL and signs and symptoms of acromegaly from baseline to weeks 12, 24 and 36	Change in scores as measured by AcroQoL, EQ-5D-5L and signs and symptoms of acromegaly from baseline to weeks 12, 24 and 36
Secondary – extension phase	
To assess the proportion of patients achieving IGF-1 <ULN at weeks 48, 60 and 72	Proportion of patients who achieved IGF-1 <ULN at weeks 48, 60 and 72
To assess the proportion of patients achieving GH <1 µg/L and IGF-1 <ULN at weeks 48, 60 and 72 by treatment with pasireotide LAR alone or with concomitant medications used to treat acromegaly	Proportion of patients who achieved GH <1 µg/L and IGF-1 <ULN at weeks 48, 60 and 72 by treatment with pasireotide LAR alone or with concomitant medications used to treat acromegaly
To assess the proportion of patients achieving GH <1 µg/L at weeks 48, 60 and 72 by treatment with pasireotide LAR alone or with concomitant medications used to treat acromegaly	Proportion of patients who achieved GH <1 µg/L at weeks 48, 60 and 72 by treatment with pasireotide LAR alone or with concomitant medications used to treat acromegaly
To evaluate the long term tolerability and safety profile of pasireotide LAR	Toxicity will be assessed using the National Cancer Institute-Common Toxicology Criteria Adverse Events version 4 (NCI-CTCAE v.4.03) and for laboratory assessments that include biochemistry, hematology, urinalysis; special safety assessments that include the regular monitoring and recording of blood glucose, insulin, HbA1c, GH and IGF-1, thyroid and liver function tests, gallbladder examinations and ECGs. Concomitant medications/Significant nondrug therapies will be assessed from study enrollment until the safety follow-up.
To evaluate the long term effect of pasireotide LAR on HRQoL and signs and symptoms of acromegaly, from baseline and week 36 to week 72	Change in scores as measured by AcroQoL, EQ-5D-5L and signs and symptoms of acromegaly from baseline to week 72 and from week 36 to week 72.

2.3 Study design and treatment

This is a phase IIIb exploratory study to assess the efficacy and safety of pasireotide in patients with acromegaly inadequately controlled with first generation somatostatin analogues. It is planned that the data from all centers that participate in this protocol will be used.

Study drug refers to pasireotide LAR (10mg, 20 mg, 40 mg or 60

mg). The brief description of the study design is given below:

Group 1 – Patients treated with octreotide LAR 30mg from the countries where octreotide LAR 40mg is approved for the treatment of acromegaly at the time of screening – Patients participate in the run-in phase.

Run-In phase (Screening to Baseline):

Patients will start treatment with octreotide LAR 40 mg every 4 weeks. Patients who have not achieved biochemical control after 3 injections can be enrolled in the study.

Core Phase (Baseline to week 36):

Patients will start treatment on pasireotide LAR 40 mg every 4 weeks until week 32. A mean GH value and IGF-1 value will be assessed every 12 weeks until week 36. The dose can be adjusted after the evaluation of biochemical control. During the core phase any acromegaly concomitant medication is prohibited.

Extension Phase (week 36 to week 76):

Patients will receive the same dose of pasireotide LAR at week 36, which is the first dose of study medication in the extension phase. At week 40 the dose can be adjusted and acromegaly concomitant medication can be added to the treatment if, patients remain uncontrolled. Patients will receive pasireotide LAR 40mg/60mg until week 68 for a total of 32 weeks in the extension phase. A mean GH value and IGF-1 value will be assessed every 12 weeks until week 72.

Safety follow-up:

After discontinuation or completion of study treatment, all patients will be followed for safety 12 weeks after the last study drug administration.

Group 2 – Patients treated with octreotide 30 mg from countries where octreotide 40mg has NOT been approved for the treatment of acromegaly at screening or patients treated with octreotide 40mg or lanreotide 120mg - Patients who do not have the run-in phase.

Core Phase (Baseline to week 36):

Same procedure to be followed as Group 1.

Extension Phase (week 36 to week 76):

Same procedure to be followed as Group 1.

Safety follow-up:

Same procedure to be followed as Group 1.

3 First interpretable results (FIR)

First interpretable results (FIR) will be provided for this trial after the completion of the core phase (After Visit 777) and after completion of the extension phase (After Visit 778).

Study outputs required to be created at the time of the FIRs will be highlighted in RAP Module 7 and marked as “Key” in the M9.1 Tracking sheet output list.

4 Interim analyses

No formal interim analysis will be performed.

5 Data included in the analysis

The analysis data cut-off for the core phase will be set as the Last Visit date for each patient (i.e., the date when the patient completes the Week 36 visit or the early discontinuation visit). All data reported in the database (scheduled, repeat and unscheduled visits) up to the cut-off data will be included.

Primary analysis will occur after all enrolled patients complete the core phase or discontinue prior to completing this phase of the trial. A CSR will be developed based on all the analyses (efficacy and safety) and results specific to the core phase of the study.

Final analysis will be conducted when all patients complete the extension phase or have discontinued the study prior to completing the extension phase of the trial.

The final CSR will include:

- Analyses and results corresponding to both core and extension phase (wherever applicable)
- Extension phase specific results.

The final CSR will include reports based on all data that has been collected up to the final CSR DBL (in general occurs 12 weeks after LPLV).

6 Statistical methods: Analysis sets

The definition of the analyses sets will remain same during the core and extension phase.

6.1 Run-in set

The Run-in set comprises of patients who:

- Must have been treated with octreotide LAR 30 mg for at least three months before screening visit from countries where octreotide LAR 40 mg is approved for the treatment of acromegaly before screening visit
- Signs informed consent and meet inclusion/exclusion criteria
- Receives octreotide LAR 40 mg every 4 weeks for 4 months after Visit 1 (Screening) to Visit 5.

6.2 Full analysis set

The **Full Analysis Set (FAS)** comprises all patients who have signed informed consent and have been treated with at least one dose of study medication (pasireotide LAR) after enrollment into the study. The protocol states that the FAS comprises all patients to whom study treatment has been assigned. The definition of the FAS in the SAP specifies that with study treatment it is meant Pasireotide LAR to avoid confusion with the second treatment drug Octreotide LAR.

6.3 Safety set

The **Safety Set** includes all patients who received at least one dose of study medication (Pasireotide LAR) with a post-baseline safety assessment. The statement that a patient has no AE constitutes a safety assessment.

The safety set will be used for all safety analyses.

6.4 Per-Protocol Set

The **Per-Protocol Set (PPS)** consists of a subset of the patients in the FAS who are compliant with requirements of the CSP. The protocol deviations criteria will be defined prior to database lock in VAP 3 and in section 7 of this document (an amendment to the RAP M3 will be considered if there are new PDs occurring in the course of the study which leads to exclusion of patients from PPS).

In section 7, detailed description of actions to be taken are described regarding data exclusion (exclusion of patients from FAS, Safety Set or PPS) corresponding to a particular protocol deviation.

General principles to be used: a protocol deviation should be classified as major, i.e., leading to exclusion of patients from PPS, only:

1. If the protocol deviation is very likely to confound the scientific analysis of the primary efficacy endpoint(s) or if it precludes any meaningful efficacy assessment,
2. If it is in direct conflict with the analysis set definition given in the title of the study (i.e., patient diagnosis, stage of disease or use of prior treatment does not correspond to the intended patient population to be studied).

More specifically, the following protocol deviations are considered project standard for major deviations:

- No disease or not the type of disease or not stage of disease required by the study protocol (e.g., incorrect diagnosis, not de novo, not refractory, not metastatic, different grade etc),
- If prior surgical/radio therapy doesn't match with protocol requirements in terms of time of previous therapy,
- If documentation of pre-baseline disease progression required and is missing,
- Patient compliance as defined as patient being evaluated for primary efficacy endpoint at least once. Patients who discontinue prior to the first efficacy assessment due to adverse events, including death, will be included.

Any other deviation leading to exclusion from the PPS will be specified in study [VAP Module 3 and section 7 of this RAP M3].

7 Protocol deviations

The following table contains the current study specific important protocol violations. The final list of PDs might deviate from this list. The table below specifies the action to be taken if any of the listed deviations occur:

Table 7-1 Protocol deviations and the corresponding actions

Protocol Deviation ID	Description used to Report PDs to HA/IRBs	Check	Identification Method Manual by FM, Manual by Study Lead 2 or Direct Hit Programming	Action

I02	Informed consent not signed at all	All required signatures are present.	Direct Hit Programming	Patient will be excluded from all analyses set
I04	GH and/or IGF-1 missing	GH/IGF-1 Lab report	Manual by FM and CTH	Patient will be excluded from PPS if GH and/or IGF-1 missing at week 36
I05	GH mean < 1ug/L or IGF-1 < 1.3x ULN	GH/IGF-1 Lab report	Manual by FM and CTH	Patient will be excluded from PPS
I06	Less than 3 months of treatment with high dose of octreotide LAR or lanreotide ATG	Patients should have confirmed treatment with 30mg octreotide in countries were the 40mg dose is not approved and 40mg dose in countries where the 40mg is approved or treatment with 120mg lanreotide ATG for 3 months prior to visit 1.	Manual by FM	Patient will be excluded from PPS
I07	Patient is a run-in failure but is enrolled in the core study	Patient should not be biochemically controlled at visit 5 or 6. (GH values less than or equal to 1 and IGF-1 > 1.3x ULN)	Manual by FM	Patient will be excluded from PPS
E01	GHR-antagonist or dopamine agonists taken < 3 months prior to visit 1	Confirm the end date of all GHR-antagonist or dopamine agonist is at least 3 months prior to visit 1.	Manual by FM	Patient will be excluded from PPS
G03	The time between the 0 minutes timepoint in the GH 5-point measurements and the 120 minutes is greater than 180 minutes	Time between the 0 minutes timepoint in the GH 5-point measurements and the 120 minutes should not be greater than 180 minutes	Direct Hit Programming	Patient will be excluded from PPS if the time between the 0 minutes timepoint in the GH 5-point measurements and the 120 minutes is greater than 180 minutes at week 36
G13	Use of other investigational drug or therapy	Patients should not use any other investigational drug or therapy during the course of the study.	Manual by FM	Patient will be excluded from all analyses from the date of use of other investigational drug or therapy
G14	Less than 3 GH 5-point measurements or missing GH assessment	Patient should not have less than 3 samples to assess 5-point mean GH or	Direct Hit Programming	Patient should be excluded from PPS if less than 3 GH 5-point measurements

		missing GH assessment		or missing GH assessment are obtained at week 36
G17	Missing IGF-1 assessment	IGF-1assessments should be done at all visits where required by the protocol	Direct Hit Programming	Patient will be excluded from PPS if there is missing IGF-1 assessment at week 36
G19	Missed visit	Patients should not miss any visit	Manual by CTH	Patient will be excluded from PPS if visit 36 is missed
S10	Up-/down-titrations of pasireotide not done as defined in protocol	Dose changes of pasireotide should be done as described in protocol e.g., patient on pasireotide LAR 40 mg who is not biochemically controlled has to be uptitrated to pasireotide LAR 60 mg at the next possible visit in the absence of any safety concerns.	Manual by FM	Patient will be excluded from PPS
D09	Patient withdrawing informed consent but not withdrawn	Patient who withdraw informed consent have to be discontinued	Manual by FM	Patient should be excluded from all analyses from the date of withdrawal of informed consent
M01	Use of medication known to affect GH or IGF-1 levels	Medication known to affect GH or IGF-1 levels are not allowed for the Core study(Visit 777)	Direct Hit Programming	Patient will be excluded from PPS from the date of use of this medication within the core phase

Table 7-2 Protocol deviation severity codes and analysis sets

Protocol deviation ID and description		Full analysis set	Safety set	Per protocol set
ID	**Text**			
I02	Informed consent not signed at all	-	-	-
I04[#]	GH and/or IGF-1 missing	+	+	-
I05	GH mean < 1ug/L or IGF-1 < 1.3x ULN	+	+	-
I06	Less than 3 months of treatment with high dose of octreotide LAR or lanreotide ATG	+	+	-
I07	Patient is a run-in failure but is enrolled	+	+	-

	in the core study			
E01	GHR-antagonist or dopamine agonists taken < 3 months prior to visit 1	+	+	-
G03#	The time between the 0 minutes timepoint in the GH 5-point measurements and the 120 minutes is greater than 180 minutes	+	+	-
G13*	Use of other investigational drug or therapy	-	-	-
G14#	Less than 3 GH 5-point measurements or missing GH assessment	+	+	-
G17#	Missing IGF-1 assessment	+	+	-
G19#	Missed visit	+	+	-
S10	Up-/down-titrations of pasireotide not done as defined in protocol	+	+	-
D09**	Patient withdrawing informed consent but not withdrawn	-	-	-
M01***	Use of medication known to affect GH or IGF-1 levels	+	+	-

+ = include in analysis set, - = exclude from analysis set, * = Patient will be excluded from all analyses from the date of use of other investigational drug or therapy, **= Patient should be excluded from all analyses from the date of withdrawal of informed consent, *= Patient should be excluded from PPS from the date of use of this medication known to affect GH and IGF-1 within core phase (on or before Week 36), #: Patient should be excluded from PPS if the deviation occurs in week 36**

If updates to this table are needed, an amendment to RAP M3 needs to be implemented prior to DBL.

8 Patient disposition, background and demographic characteristics

8.1 Patient disposition: Run-in and screen failure

The following summaries will be provided:

- Number (%) of patients screened
- Number (%) of patients screened but did not entered run-in phase (usual screen failure) and reason for not continuing
- Number (%) of patients who entered run-in phase
- Number (%) of patients who discontinued during the run-in phase
- Number (%) of patients who entered the core phase

The patients who were screened and the run-in set will be used for the above disposition.

8.2 Patient disposition: FAS

The FAS will be used for presenting patient disposition. The following summaries will be provided:

- Number (%) of patients who completed the core phase
- Number (%) of patients who entered the extension phase
- Number (%) of patients who completed the extension phase
- Number (%) of patients who discontinued and reason for discontinuation at any time prior to end of study (Week 72, Visit 778)
- Number (%) of patients who discontinued and reason for discontinuation prior to week 36 (core phase, Visit 777)
- Number (%) of patients who discontinued and reason for discontinuation prior to week 72 (extension phase, Visit 778) after completing the core phase

8.3 Protocol deviation summaries

The number and percentage of patients in the FAS with any CSR reportable protocol deviation will be tabulated by major protocol deviations (excluded from PPS) and minor protocol deviations. Listing will also be provided for all the protocol deviations based on FAS.

8.4 Background and demographic characteristics

All demographic characteristics and background data (e.g., age, gender, race, GH levels, standardized IGF-1 levels) will be summarized and listed in the FAS.

Qualitative characteristics (e.g., gender) will be summarized by means of contingency tables. Quantitative variables (i.e., age, weight, BMI) will be summarized by appropriate descriptive statistics (i.e., mean, SD, median, minimum, maximum).

Information on aryl hydrocarbon receptor-interacting protein (AIP) mutation and MRIs performed will also be summarized and listed.

Baseline diabetic status will be summarized. The status will be defined as follows:

- Diabetic: Patients were taking anti-diabetic medication at baseline, or prior past medication history of diabetes mellitus or baseline HbA1C >=6.5% or baseline fasting glucose >=126 mg/dL or 2-H plasma glucose (during oGTT at screening visit) of greater or equal 200 mg/dL (>=11.1 mmol/L)
- Pre-diabetic: Patients with 100 mg/dL <=baseline FBG< 126 mg/dL or 5.7% <=baseline HbA1c<6.5% or 140 mg/dL (i.e., 7.8 mmol/L) <= 2-H plasma glucose (during oGTT at screening visit) < 200 mg/dL (i.e., < 11.1 mmol/L)
- Non-diabetic: Patients not qualifying as diabetic or pre-diabetic and with baseline FBG is not missing and < 100 mg/dL and baseline HbA1c is not missing and <5.7% and and 2-H plasma glucose (during oGTT at screening visit) is not missing and < 140 (i.e., less than 7.8 mmol/L)
- Missing − patients with no prior history of DM and no history of antidiabetic medication, both FBG and HbA1c are missing.

8.5 Medical history

The FAS will be used for all medical history summaries and listings including medical history for acromegaly. Medical history and current medical conditions will be summarized

separately by primary system organ class (SOC) and preferred term (PT) based on latest available Medical Dictionary for Regulatory Activities (MedDRA) dictionary version at time of database lock. The MedDRA version used for reporting the study will be specified as a footnote in the related tables/listings. Listings will also be provided.

8.6 Prior acromegaly therapy

Prior therapy for acromegaly including surgery, radiation and medication will be summarized and listed based on the FAS

8.7 Other

All data collected at baseline such as child bearing potential, pregnancy test results and tumor volume (tumor evaluation using MRI) will be listed as required based on the FAS.

9 Extent of exposure

9.1 Study drug

Study drug refers to pasireotide LAR (10 mg, 20 mg, 40 mg or 60 mg).

9.2 Study medication

The safety set will be used for all summaries and listings of study medication.

Duration of exposure to study drug, number of injections taken and number of patients with dose change and/or dose delay along with reasons for dose change/dose delay, will be summarized by appropriate descriptive statistics. In addition, number of injections will be summarized categorically (categories to be specified in RAP Module 7).

All doses of the study drug along with reasons for dose change/delay will be listed.

The above summaries and listings will be provided for overall study period (core + extension phase), and separately for core phase and extension phase

9.3 Exposure

The following definitions will be used corresponding to study drug pasireotide LAR only:

Core phase:

Study drug start date is defined as the first date when a non-zero dose of study drug (pasireotide LAR) was administered and recorded on the Drug Administration Record (DAR) CRF page.

Study drug end date is defined as the last date when a non-zero dose of study drug (pasireotide LAR) was administered in the core phase of the study.

Extension phase:

Study drug start date is defined as the first date when a non-zero dose of study drug (pasireotide LAR) was administered during the extension phase and recorded on the Drug Administration Record (DAR) CRF page.

Study drug end date is defined as the last date when a non-zero dose of study drug (pasireotide LAR) was administered in the extension phase of the study.

Duration of exposure in core phase (in weeks) will be calculated as:

{min(study drug end date in core phase + 27 days; death date) – study drug start date in core + 1 day} / 7 days.

Duration of exposure in core phase (in months) will be calculated as:

{min(study drug end date in core phase + 27 days; death date) – study drug start date in core + 1 day} / 30.4375.

Cumulative dose (mg): total dose of study drug taken by a patient in the core phase

Dose intensity (DI) (mg/month): cumulative dose (mg) / duration of exposure (months).

Duration of exposure in extension phase (in weeks) will be calculated as:

{min(study drug end date in extension phase + 27 days; death date) – study drug start date in core phase + 1 day} / 7 days.

Duration of exposure extension phase (in months) will be calculated as:

{min(study drug end date in extension phase + 27 days; death date) – study drug start date in extension phase + 1 day} / 30.4375

Cumulative dose (mg): total dose of study drug taken by a patient in the extension phase

DI (mg/month): cumulative dose (mg) / duration of exposure (months).

The duration includes periods of temporary interruption for any reason.

Duration of exposure will be presented overall and for up-titrated Pasireotide LAR 60 mg (highest dose received during the trial.)

In addition, the number of patients on maximum dose during the core phase (20, 40 or 60 mg) will be provided

10 Prior and concomitant medication

Prior and concomitant therapy is defined as all interventions (therapeutic treatments and procedures) besides the study treatment that are administered to a patient preceding or coinciding with the study assessment period.

Prior and concomitant medications and significant non-drug therapies for acromegaly and excluding acromegaly will be listed and summarized separately in the safety set.

Summary on prior medications and significant non-drug therapies (for acromegaly and excluding acromegaly) will be provided only for the core phase. The concomitant medications and significant non-drug therapies (for acromegaly and excluding acromegaly) will be provided for overall study period (core + extension phase) and separately for core phase and extension phase.

Separate summaries on prior and concomitant anti-diabetic medication after start of study drug (pasireotide LAR) will be provided for over study period and separately for core phase and extension phase.

Medications will be classified as prior or concomitant based on the following rules and will be coded using the WHO Drug Reference List to allow for categorization by preferred term:

- Prior medication are medications that started before the first dose of study drug regardless of whether the medication ended before or after the first dose of study drug.

- Concomitant medications are medications that started on or after the first dose of study drug, or started before the first dose of study drug and continued after the first dose of study drug.

In addition to categorizing medication data by preferred term, drugs will be classified according to their ATC classification in order to present and compare how they are being utilized. The ATC classification allows summarization of medications by a high-level common drug class.

A separate listing will be provided for patients who take concomitant medication related to prolonging the QT interval and therefore at the risk of ventricular arrhythmia, Torsades de

Pointes and sudden death for the overall study period (core + extension phase). The listing will only include the concomitant medications (with dose unit and frequency route) related to QT prolongation taken at the time of QT prolongation along with the ECG intervals. The patients who have > 60 ms QTcF change from baseline or QTcF > 480 ms will be flagged.

11 Medications known to affect GH and IGF-1 levels

During the core phase any acromegaly concomitant medication is prohibited. Medication taken in core phase (other than study drug) and known to affect GH and IGF-1 levels will be identified as protocol deviations. Patient will be excluded from Per-Protocol set for all efficacy analysis from the date of use of this medication within the core phase (see section 7 of this RAP M3 for more details). A periodic clinical review of individual study data will be performed in order to identify medications known to affect GH and IGF-1 levels.

Medications known to affect GH or IGF-1 levels will be allowed only during the extension phase (starting from week 40) for patients who do not achieve biomedical control in the core phase.

The following concomitant medications will be used to treat acromegaly (WHO dictionary code in brackets):

- Somatostatin analogs (H01CB)
- Dopamine agonists (N04BC)
- Growth hormone receptor antagonists (H01AX)

For patients who take concomitant medications known to affect GH or IGF-1 levels during the core phase, a listing will be provided for those patients along with only the concomitant medications known to affect GH or IGF-1 levels.

In the extension phase, if there are more than 10 patients who take concomitant medications known to affect GH or IGF-1 levels, a summary table will be provided for those patients with medication data. If not, then only a listing will be provided.

12 Statistical methods for run-in population

The **run-in set** will be used to find the proportion of responders (GH < 1 μg/L and IGF-1 < ULN) among patients in Group 1 during the run-in phase.

Also listings will be provided for the patients who discontinues during the run-in phase or are considered as screen failures (after the completion of run-in phase). The listings will include the following: Demography, relevant medical history/current medical conditions, prior/concomitant medications for acromegaly and excluding acromegaly, prior history of acromegaly, vital signs, symptoms of acromegaly, laboratory assessments (hematology, chemistry, LFTs, Hepatitis screening, coagulation, hyperglycemia related tests, thyroid and hormones, urinalysis, IGF-1, GH, pregnancy tests), ECG, gallbladder, adverse events and study drug administration of octreotide LAR 40 mg.

13 Statistical methods for efficacy evaluation

13.1 Analyses time points

The main analysis time point will be the 36 week time point (the time when all patients will complete Week 36 visit or discontinued early). The primary and some secondary endpoints (during the core phase, see section 13.3.1) will be analyzed at that time point. The other secondary endpoints related during the core phase will be analyzed at week 12 or 24. The secondary endpoints related during the extension phase will be analyzed at week 48, 60, or 72.

13.2 Primary efficacy evaluation

The primary objective is to obtain the proportion of patients achieving biomedical control defined as mean GH levels < 1 µg/L and IGF-1 < ULN at 36 weeks.

The trial is exploratory in nature and no formal hypothesis testing is planned.

The primary efficacy variable is the proportion of patients with a reduction of mean GH levels to < 1 µg/L and IGF-1 < ULN at 36 weeks. Two-sided, exact 95% confidence interval for the proportion will also be provided.

The analysis will be done on FAS and on PPS.

13.2.1 Graphical presentation of results

Plots for mean (+/- SE) of 5-point mean GH and standardized IGF-1 by visit will be provided for the core phase and overall study period (core + extension phase).

13.2.2 Handling of missing values/censoring/discontinuations

If a patient has less than three samples for the assessment of the 5-point mean GH from the 2-hour profile, then the mean GH will be considered as missing. In addition, if GH and IGF-1 measurements are taken after 35 days from the date of any injection of study drug (from the scheduled dose date), the values will be considered as missing (the rationale has been adopted based on study CSOM230C2402). For a patient with missing values of mean GH or IGF-1 at 36 weeks or who withdraws earlier from the study will be considered as a non-responder.

13.2.3 Sensitivity analysis by imputing missing values

A sensitivity analysis will be added for the primary efficacy variable by imputing missing values of mean GH and IGF-1 at week 12, week 24 and week 36 of the core phase using the Last Observation Carried Forward (LOCF) method. Values at the screening and/or baseline visit will not be carried forward (e.g., patient with only values at the screening and/or baseline visit will be considered as a non-responder). At each time point (i.e., week 12, week 24 and week 36) the proportion of patients with a reduction of mean GH levels to < 1 µg/L and IGF-1 < ULN with two-sided, exact 95% confidence interval for the proportion will be provided.

The analysis will be done on FAS.

13.2.4 Supporting analysis of Primary Objective

The following supportive analyses for the primary efficacy endpoint will be performed on the FAS.

- The proportion of patients who achieved GH < 1 µg/L and IGF-1 < ULN at week 36 among two sub-groups of patients, those having GH level at screening between 1 µg/L and 2.5 µg/L, and those having GH level > 2.5 µg/L at screening, will be reported along with their two-sided exact 95% confidence interval.
- The proportion of patients who achieved GH < 1 µg/L and IGF-1 < ULN at week 36 among two sub-groups of patients, those receiving 20 mg of pasireotide LAR, 40 mg of pasireotide LAR and 60 mg of pasireotide LAR at week 36 will be reported along with their two-sided exact 95% confidence interval.

13.3 Secondary objectives

The secondary efficacy analyses will be performed on the FAS. The same rule of handling missing values for GH and IGF-1 variables as specified in the analyses of the primary efficacy variable will be used.

13.3.1 Secondary objectives – Core phase

13.3.1.1 To assess the changes in mean GH from study baseline to week 36

Descriptive summaries of actual and percentage change in GH from study baseline to week 36 values will be provided.

13.3.1.2 To assess the changes in standardized IGF-1 from study baseline to week 36

Descriptive summaries of actual and percentage change in standardized IGF-1 from study baseline to week 36 values will be provided.

13.3.1.3 To assess the proportion of patients achieving GH < 1 µg/L and IGF-1 < ULN at weeks 12 and 24 overall and by GH level at screening

Proportion of patients who achieved GH < 1 µg/L and IGF-1 < ULN at week 12 and 24 will be reported along with its corresponding 95% confidence interval for all patients and also among patients, having GH level at screening between 1 µg/L and 2.5 µg/L, and patients having GH level at screening > 2.5 µg/L.

13.3.1.4 To assess the proportion of patients achieving GH < 1 µg/L at weeks 12, 24 and 36, overall and by GH level at screening

Proportion of patients who achieved GH < 1 µg/L at week 12, 24 and 36 will be reported along with its corresponding 95% confidence interval for all patients and also among patients, having GH level at screening between 1 µg/L and 2.5 µg/L, and patients having GH level at screening > 2.5 µg/L.

13.3.1.5 To assess the proportion of patients achieving IGF-1 levels < ULN at weeks 12, 24 and 36, overall and by GH level at screening

Proportion of patients who achieved IGF-1 < ULN at week 12, 24 and 36 will be reported along with its corresponding 95% confidence interval for all patients and also among patients, having GH level at screening between 1 µg/L and 2.5 µg/L, and patients having GH level at screening > 2.5 µg/L.

13.3.1.6 To evaluate the effect of pasireotide LAR on HRQoL, EQ-5D-5L and signs and symptoms of acromegaly from baseline to weeks 12, 24 and 36

Descriptive statistics, including mean, median, standard deviation, minimum and maximum, will be presented for all patient-reported outcomes (PRO) to describe actual standardized scores as measured by HRQoL and EQ-5D-5L index scores and EQ-VAS scores. For each acromegaly symptoms (ring size, headache, fatigue, perspiration, paresthesias, osteoarthralgia), descriptive summaries of actual and changes will be provided.

For each of the PRO variables (AcroQoL score (total score, physical sub-score and psychological sub-score [psychological/physical appearance and psychological/personal relations]), EQ-5D-5L utility index and EQ-5D-5L VAS score):

- Change in PRO scores for all patients from baseline to weeks 12, 24 and week 36.

For the self-reported signs and symptoms (ring size, headache, fatigue, perspiration, paresthesias, osteoarthralgia):

- Change in symptom severity scores (for each sign and symptom) from baseline to weeks 12, 24 and 36.
- Shift tables from baseline to most extreme post-baseline value up to week 36 will also be presented for acromegaly symptoms except ring size.

13.3.2 Secondary objectives – Extension phase

13.3.2.1 To assess the proportion of patients achieving IGF-1 < ULN at weeks 48, 60 and 72 by treatment with pasireotide LAR alone or with concomitant medications used to treat acromegaly

Proportion of patients who achieved IGF-1 < ULN by treatment with pasireotide LAR alone or with concomitant medications used to treat acromegaly will be reported separately (if there are 10 more patients with concomitant medications used to treat acromegaly in extension phase) along with its two-sided 95% confidence interval at week 48, 60 and 72.

13.3.2.2 To assess the proportion of patients achieving GH < 1 µg/L and IGF-1 < ULN at weeks 48, 60 and 72 by treatment with pasireotide LAR alone or with concomitant medications used to treat acromegaly

Proportion of patients who achieved GH < 1 µg/L and IGF-1 < ULN by treatment with pasireotide LAR alone or with concomitant medications used to treat acromegaly will be reported separately (if there are 10 more patients with concomitant medications used to treat acromegaly in extension phase) along with its corresponding 95% confidence interval at weeks 48, 60 and 72.

13.3.2.3 To assess the proportion of patients achieving GH < 1 µg/L at weeks 48, 60 and 72 by treatment with pasireotide LAR alone or with concomitant medications used to treat acromegaly

Proportion of patients who achieved GH < 1 µg/L by treatment with pasireotide LAR alone or

with concomitant medications used to treat acromegaly will be reported separately (if there are 10 more patients with concomitant medications used to treat acromegaly in extension phase) along with its corresponding 95% confidence interval at weeks 48, 60 and 72.

13.3.2.4 To evaluate the long term effect of pasireotide LAR on HRQoL, EQ-5D-5L and signs and symptoms of acromegaly, from baseline and week 36 to week 72

Descriptive statistics, including mean, median, standard deviation, minimum and maximum, will be presented for all patient-reported outcomes (PRO) to describe actual standardized scores as measured by HRQoL and EQ-5D-5L index scores and EQ-VAS scores. For each acromegaly symptoms (ring size, headache, fatigue, perspiration, paresthesias, osteoarthralgia), descriptive summaries of actual and changes will be provided.

For each of the PRO variables (AcroQoL score (total score, physical sub-score and psychological sub-score [psychological/physical appearance and psychological/personal relations]), EQ-5D-5L utility index and EQ-5D-5L VAS score):

- Change in PRO scores from
    - baseline to week 36
    - baseline to week 72
    - week 36 to week 72

For the self-reported signs and symptoms (ring size, headache, fatigue, perspiration, paresthesias, osteoarthralgia):

- Change in symptom severity scores (for each sign and symptom) from
    - baseline to week 36
    - baseline to week 72
    - week 36 to week 72
- Shift tables from baseline to most extreme post-baseline value up to week 72 will also be presented for acromegaly symptoms except ring size.

13.3.3 Graphical presentation of results

Plot of mean values of AcroQoL score by visit (total score, physical sub-score and psychological sub-score [psychological/physical appearance and psychological/personal relations]), EQ-5D-5L (utility index and VAS score) by visit will be provided. A multiple bar chart corresponding to proportion of patients to each response categories for the EQ-5D dimension will be provided (layout will be specified in RAP Module 7). The plots will be considered for the overall study period (core + extension phase).

14 Statistical methods for safety analysis

Safety assessments will consist of monitoring and recording all adverse events (AEs), including serious adverse events (SAEs), the regular monitoring of hematology (including coagulation parameters), blood chemistry (including fasting blood glucose), glycosylated hemoglobin, fasting serum cortisol, plasma adrenocorticotropic hormone, liver and thyroid function tests, urinalysis, injection site reactions, physical examinations including vital signs, gallbladder ultrasound, ECGs and body weight.

All the safety analysis will be based on safety set.

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

1. pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
2. on-treatment period: from day of first dose of study medication to 84 days after last dose of study medication
3. post-treatment period: starting at day 84 days + 1 after last dose of study medication

For the core phase, all listings and tables will be presented overall and by maximum dose given. For AEs of special interest, tables will be presented by the given dose as well (AE starts or worsens while the patient is being treated at that dose level).

For the extension phase, all listings and tables will be presented overall and by type of treatment (monotherapy, combination dopamine agonist, and combination with GH receptor antagonist).

14.1 Adverse events (AE)

14.1.1 Coding of AEs

All adverse events will be coded using the latest MedDRA coding dictionary that provides the system organ class and preferred term information available during the time of required analyses.

14.1.2 Grading of AEs

Adverse events will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

14.1.3 General rules for AE reporting

Summary tables for adverse events (AEs) from the study will include AEs that started or worsened in the period from study drug start date up to the patient's last day on the study (inclusive), but no later than 84 days after study drug end date. The incidence of treatment-emergent AEs (new or worsening from baseline) will be summarized by SOC and/or PT, severity (based on CTCAE grades), type of AE and relation to study treatment. If an AE deteriorates or improves over time, new event will be reported accordingly with new severity.

Deaths will be listed and summarized by cause of death.

14.1.4 AE summaries

Adverse events will be summarized and listed in the following way:

- AEs, regardless of study drug relationship
- AEs, suspected to be study drug related
- SAEs, regardless of study drug relationship
- SAEs, suspected to be study drug related
- AEs leading to discontinuation/dose adjustment or interruption/additional therapy
- AEs of special interest
- Deaths by primary system organ class and preferred term
- Hyperglycemia-related AEs by diabetic status at baseline, by preferred term and maximum CTC grade

Adverse events will be presented overall and for up-titrated Pasireotide LAR 60 mg (highest dose received during the trial).

The presentation of the adverse events summary based on SOC, PT, maximum grade will be specified in appropriate layouts in RAP Module 7.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment-emergent adverse events which are not serious adverse events with an incidence greater than 5% and on treatment-emergent 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.

14.1.5 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.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 (in [Cabinets/CREDI Projects/S/SOM230C/Administrative files/CIS (Clinical Information Sciences)/Biostatistics/SOM230C_AESI_MedDRA xx x<use the latest available version>_ddMMMyyyy.xls<use the latest available data set>]) will be used.

The following summary will include the following:

- AESI, regardless of study drug relationship, with maximum grade, suspected to be study drug related, SAEs, leading to discontinuation and requiring dose adjustments

14.2 Laboratory values

The severity grades for laboratory values are derived using NCI/NIH Common Toxicity Criteria (CTC). A severity grade of zero will be assigned when the value is within normal limits. All laboratory values will be converted into SI units. However, blood glucose will also be presented in mg/dL and assessed using the ADA criteria 2010.

The following laboratory parameters will be collected:

Table 14.2-1 Local or Central Clinical Laboratory Parameters Collection Plan

Test category	Test name
Hematology (central)	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, RBC Morphology with differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)
Clinical Chemistry (central)	Bicarbonate, Calcium, Chloride, Creatinine*, Creatine Kinase, Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, α-amylase, Lipase, Lactic Dehydrogenase (LDH), Magnesium, Sodium, Potassium, Prolactin
Liver Function Tests (Central)	ALT, AST, Total bilirubin (total bilirubin should be differentiated into direct and indirect reacting bilirubin if total bilirubin is increased > 2 × ULN), Albumin, ALP and GGT
Hepatic Screening (Central)	HbsAg, AntiHCV
Hyperglycemia related test (Central)	Fasting blood glucose, Glycosylated Hemoglobin (HbA1C), oGTT (insulin and plasma glucose)

Coagulation (central)	Prothrombin time (PT) or International normalized ratio (NR), Partial thromboplastin time (PTT), Activated partial thromboplastin time (APTT)
Thyroid and hormones (central)	T4 [free], TSH, Plasma Adrenocorticotropic Hormone (ACTH), Fasting Serum Cortisol

Test category	Test name
Urinalysis (local)	Macroscopic Panel (Dipstick) (Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, pH, Protein, Specific Gravity)
Additional tests (central)	Insulin-like growth factor 1 (IGF-1), Growth Hormone (GH)
Pregnancy test	Urine (dipstick) and serum B-hCG

(*) Q2 Serum Creatinine Issue

An equipment malfunction issue was identified with respect to one of the Beckman Coulter AU5400 units in the Valencia Laboratory. Serum Creatinine samples analyzed between 01-Oct-2016 to 13-Jan-2017 were impacted. Sample results that could not be repeated for this study (because there was no backup sample) will be annotated in the clinical data base as reported but unreliable and therefore will be considered unreliable. Data will remain in the clinical data base, but will not be used as part of CSR statistical analyses. These unreliable results will appear in the listings, but they will be excluded from the biochemistry shift table analyses. Results obtained which were repeated and confirmed within 10% of the original samples will be used for statistical analyses and listed. Results obtained that were repeated and not within 10% of the original samples will be replaced in the clinical data base by the retest values and will be used for statistical analyses and listed.

Summaries for laboratory parameters will include all laboratory assessments collected in the core and extension phase.

For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used. In the unlikely case when a local laboratory normal range overlaps into the higher (i.e. non-zero) CTC grade, the laboratory value will still be taken as within normal limits and assigned a CTC grade of zero. 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.

The following summaries will be produced for the laboratory data (by laboratory parameter) corresponding to on-treatment period for post-baseline values:

- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value,
- For laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high classification to compare baseline to the worst on-treatment value,
- Number and percentage of patients meeting individual and composite Hy's Law criteria (i.e. ALT > 3 × ULN with concurrent total bilirubin >2 × ULN, without increases in alkaline phosphatase and no other cause(s) identified for the abnormal findings) for liver injury (each patient will be counted only for the worst observed post baseline value),
- Fasting blood glucose (FBG) [< 100 mg/dL, ≥ 100 - < 126 mg/dL and ≥ 126 mg/dL] using the ADA (2010) classifications to compare baseline to last on-treatment value.
- For the shift tables for blood glucose (HbA1C) cut-offs similar to the ADA (2010) will be used, defined as (<5.7%, >=5.7% - <6.5%, >=6.5 - <8% and >=8%) to compare baseline to the last on-treatment value,
- Summary of responders at week 36 (primary endpoint) by baseline diabetic status (specified in section 8.4 of this RAP M3)
- Summary of change from baseline to week 36 in HbA1C by primary response at week 36 (primary endpoint),
- Summary of change from baseline to week 36 in FBG by primary response at week 36 (primary endpoint)

The following listings will be produced for the laboratory data:

- Listings of patients with laboratory values outside the laboratory reference ranges with

values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory reference ranges,

- Listings of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges,

- Listing of patients with notable laboratory abnormalities (i.e., newly occurring CTCAE grade 3 or 4 laboratory toxicities).

14.2.1 Graphical presentation of results

Plots for mean (+/- SE) of FBG and HbA1c by visit will be provided for the core phase and overall study period (core + extension phase).

14.3 Vital signs and weight

Vital signs (blood pressure, heart rate and body temperature) and weight will be summarized and listed by visit and treatment group. Patients with clinically notable vital sign values will be flagged in the listing.

The criteria for clinically notable values are defined as follows:

Clinically notable elevated values

- Systolic BP: ≥ 180 mmHg and an increase ≥ 20 mmHg from baseline,
- Diastolic BP: ≥ 105 mmHg and an increase ≥ 15 mmHg from baseline,
- Body temperature: ≥ 39.1°C,
- Weight: Increase from baseline of ≥ 10%,
- Pulse rate: ≥ 100 bpm with increase from baseline of > 25%.

Clinically notable below normal values

- Systolic BP: ≤ 90 mmHg and a decrease ≥ 20 mmHg from baseline,
- Diastolic BP: ≤ 50 mmHg and a decrease ≥ 15 mmHg from baseline,
- Body temperature: ≤ 35°C,
- Weight: Decrease from baseline of ≥ 10%,
- Pulse rate: ≤ 50 bpm with decrease from baseline of > 25%.

The following summaries will be produced for each vital sign parameter:

- Vital signs shift table based on notable values

14.4 ECG

The following analyses will be performed for VR, PR, QT intervals and QRS duration, ventricular rate, and QTcF (Fridericia's formula) during the on- treatment period:

- Summary statistics at baseline and all scheduled post-baseline time points,
- Summary statistics of changes from baseline at each scheduled post-baseline time point,
- Listing of ECG data (scheduled and unscheduled visits).

Number (%) of patients with a notable and newly occurring QT interval, based on QTcF will be summarized. ECG shift table based on notable values from baseline to worst post-baseline value will be summarized. Notable criteria for QT/QTcF include:

- > 450 ms at any post-baseline scheduled time point and ≤ 450 ms at baseline,
- > 480 ms at any post-baseline scheduled time point and ≤ 480 ms at baseline,

- > 500 ms at any post-baseline scheduled time point and ≤ 500 ms at baseline,
- An increase from baseline > 30 ms at any post-baseline scheduled time point,
- An increase from baseline > 60 ms at any post-baseline scheduled time point.

Notable criteria for PR, QRS and VR include:

- A new PR > 200 ms at any post-baseline scheduled time point,
- An increase from baseline > 25% and PR > 200 ms at any post-baseline scheduled time point,
- A new QRS > 120 ms at any post-baseline scheduled time point,
- An increase from baseline > 25% and QRS > 120 ms at any post-baseline scheduled time point,
- An increase from baseline > 25% and VR > 100 bpm at any post-baseline scheduled time point,
- A decrease from baseline > 25% and VR < 50 bpm at any post-baseline scheduled time point,

A patient with multiple occurrences of a notable QT interval or a newly occurring ECG abnormality is counted only once in that category.

Patients with notable QT interval values and newly occurring qualitative ECG abnormalities will be flagged in the listings.

No imputation of missing data will be performed.
The formulae used to calculate the QT interval corrected for heart rate is:

- Fridericia's formula, $QTcF = QT/\sqrt[3]{RR}$

14.5 Gallbladder ultrasound

Gallbladder data at each visit will be summarized and listed by treatment group. Shifts from baseline to last post-baseline value will be presented for each individual item.

15 Sample size and power considerations

The sample size calculation was based on the primary endpoint (mean GH < 1 µg/L and IGF-1 < ULN at week 36). A sample size of 100 patients was chosen to enable the estimation of proportion of patients who achieved biochemical control at week 36 with pasireotide 40-60 mg as 15%, with a precision of 7% for the associated asymptotic two-sided 95% confidence interval.

Considering a drop-out rate of 10%, the sample size required is 112.

Sample size calculations were performed using PASS 2008 software.

16 References

ADA Diagnosis and Classification of Diabetes Mellitus (2010) Diabetes Care, volume 33, supplement 1, January 2010.

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Clinical Development

SOM230/pasireotide

CSOM230C2413

Appendix 16.1.9: Documentation of statistical methods

Document type: Clinical Study Report - Appendix 16.1.9

17 Appendix 16.1.9 Documentation of statistical methods

This section of the RAP document presents further detail about the statistical methods not given in section 9.7 of the Clinical Study Report (CSR).

17.1 Dates and time windows

17.1.1 Study drug start and end date

Study drug start date is defined as the first date when a non-zero dose of study drug was administered and recorded on the Drug Administration Record (DAR) CRF page. Similarly, **study drug end date** is defined as the last date when a non-zero dose of study drug was administered and recorded on the DAR CRF page.

Note:

- Study drug start date definition will remain same irrespective of whether any analyses are done in core or extension phase.
- Study drug end date definition will change, i.e.,
  - for any analyses in core phase where study drug end date definition is required, it will be defined as the last date when a non-zero dose of study drug (pasireotide LAR) was administered in the core phase of the study.
  - for any analyses in extension phase where study drug end date definition is required, it will be defined as the last date when a non-zero dose of study drug (pasireotide LAR) was administered in the extension phase of the study.

17.2 Study day

Study day will be calculated as (event date – study drug start date + 1 day) for events that occurred on or after study drug start date (e.g. lab samples, AEs). For events prior to study drug start date (e.g. time of diagnosis), study day will be negative and calculated as (event date – study drug start date). Note that study drug start date is study day 1 and the day before study drug start date is study day -1 (i.e. no study day 0).

For patients who never took study drug, the date of inform consent signed will replace study drug start date in the above formulas (i.e. study day 1 is the date of inform consent signed). Due to the study drug dosing schedule, one month will be considered as 28 days. However, for ‘time since event’ data (e.g. medical history), one month will be considered as 365.25/12 days for events that occurred prior to study day 1.

17.3 End of treatment

Patients who discontinue study treatment before visit 777 (week 36) in the core phase and visit 778 (week 72) in the extension, should be scheduled for a visit as soon as possible to have all assessments listed for the 777 or 778 visits performed (see Table 7-1, Table 7-2, Table 7-3 of the protocol). A Study Completion CRF page should be completed, giving the date and reason for stopping study treatment. At a minimum, all patients who discontinue study treatment, including those refuse to return for a final visit, will be contacted for safety evaluations during the 84 days following the last dose of study treatment.

If such withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the Study Completion CRF page (the reasons are listed in Section 7.1.5 of the protocol).

17.4 Baseline definition

For efficacy and safety evaluations, baseline is defined as the last available value (or assessment) on or before the date of start of study treatment.

Moreover, for ECG, if several lab measurements are taken at pre-dose on Day 1 the last value will be used as baseline.

If a patient has no value (or assessment) as defined above, then baseline will be considered missing for that efficacy and/or safety evaluation.

17.5 Time windows

Summaries and analyses will be presented, when applicable, by (and/or based on data from) the actual visit. Time windows will not be considered.

The visits 777 (End-of-Core-Study visit) and 778 (End-of-Extension-Study visit) are scheduled when the patient decides (or is mandated by the protocol) to discontinue from the study. If such a visit happens neither too soon nor too late after the actual last scheduled visit then it will be mapped to the next scheduled visit that would have occurred had the patient continued in the study. Otherwise the early discontinuation visit will not be mapped to any scheduled visit.

The early discontinuation visit will be considered to have occurred neither too soon nor too late after the actual last scheduled visit if number of days between the two visits is:

- At least half of the way between the patients' actual last scheduled visit and the next planned scheduled visit, and
- No more than the total of the planned gap between the patient's actual last visit and next scheduled visit and half of the way between the patients' next two planned

For example, if the patients' last actual scheduled visit is Visit 12, then the next two planned visits (ignoring visit 7) would have been Visit 8 and Visit 9 if this patient had not discontinued early. Thus, the study completion visit will be mapped to Visit 8 only if it occurs between 14 days (Day 112 – Day 84)/2 and 42 days (28 + (Day 140 – Day 112)/2) after Visit 12.

If the above condition is not met, then the study completion visit will not be mapped to any scheduled visit.

17.5.1 Evaluation time window

There is a +/- 2 day window for the visits but the labs must be taken the same day as the visit.

MRI and gallbladder ultrasound data collected within +/- 35 days from the date of visit is allowed. Pre-dose ECG collected within 24-hours prior to injection of study drug is allowed. Unless otherwise noted, values outside these time windows will not be included in the analyses.

17.6 Concomitant medications

Concomitant medications with a known risk for Torsade des Pointes are prohibited and patients are required to discontinue the study prior to starting the respective medication with known risk for Torsade des Pointes. Concomitant medications with a possible risk for Torsade des Pointes are permissible but should be avoided wherever possible. A regularly updated list of medications with known/possible risk for Torsade des Pointes or congenital long QT is available under https://crediblemeds.org/index.php

The description used to report PD: **"Patient taking a QT prolonging medication with known risk factors for torsade de pointes and not withdrawn"** with PD code: D05 can be used to filter out the patients who have taken concomitant medications with a known risk for Torsade des Pointes based on the listings of the medications with known risk for Torsade des Pointed being provided by the clinical team.

For anti-diabetic medication, any medication with ATCCODE = A10 will be considered as anti-diabetic medication.

17.7 General definitions, conventions and methods

17.7.1 Standardized IGF-1 values

The normal range for IGF-1 is dependent on age and sex. Therefore, unless noted otherwise, standardized IGF-1 values will be reported. Standardized IGF-1 values are defined as:

Standardized IGF-1 = IGF-1 value / ULN

where ULN is the corresponding age- and sex-adjusted upper limit of normal.

Note that standardizing the IGF-1 values has no effect on the percentage change from baseline calculation as this calculation is independent of the ULN.

17.7.2 Symptoms of acromegaly

Ring size will be measured at the fourth digit of the non-dominant hand. If a patient has a fourth digit size exceeding the highest size, the fifth digit of that hand will be used for initial and follow-up investigation. The investigator will also ask the patient to score the following symptoms of acromegaly: headache, fatigue, perspiration, paresthesias, osteoarthralgia according to a five-point score scale (0=absent, 1=mild, 2=moderate, 3=severe, 4=very severe).

17.7.3 Quality of life

The AcroQoL is a valid and reliable disease-specific patient-reported outcome (PRO) questionnaire designed to assess quality of life in patients aged 18 to 70 years old with acromegaly (Badia, et al 2004).

The questionnaire is uni-dimensional and contains 22 items divided in two scales: physical aspects (eight items) and psychological aspects (14 items). The latter scale is also divided in two sub-scales: one to evaluate physical appearance, and the other to evaluate the impact of the disease on the personal relationships of the patient (seven items each).

Results of the AcroQoL are reported as:

- A total score (22 items)
- A physical sub-score (8 items)
- A psychological sub-score (14 items)

The psychological sub-score is further divided into two sub-scores:

- A psychological/physical appearance (7 items)
- A psychological/personal relations (7 items)

Items are scored on a five point Likert-type scale assessing either the frequency of occurrence (always, most of the time, sometimes, rarely, or never) or the degree of agreement with the items (completely agree, moderately agree, neither agree nor disagree, moderately disagree, completely disagree). For the purpose of the clinical trial, the recall period of the AcroQoL has been modified to 4 weeks.

The total score and sub-scores will be calculated using the following formula established by the tool developer (Badia, et al 2004):

$((X - Y) / 4Y) \times 100$

X = sum of the scores for individual items (between 1 and 5 for each item)

Y = number of individual items included in above sum (i.e. 22 for the total score, 8 for the physical sub-score, 14 for the psychological sub-score, 7 for the sub-score 'appearance' and 'personal relations')

If more than 25% of items are not completed, then the results for that patient will be considered invalid. Specifically, results for a particular score/sub-score will not be included for analysis if the number of missing items exceeds:

- Five for the total score,
- Two for the physical dimension,
- Three for the psychological dimension,
- One for each of the psychological sub-dimensions

17.8 Health status

Health status will be assessed using the EQ 5D-5L. The EQ- 5D-5L has two components– the EQ-5D-5L descriptive system and the EQ-5D-5L visual analogue scale (VAS) (Herdman M et al 2011) The descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension has 5 levels: ' no problems', 'slight problems', 'moderate problems', 'severe problems' and 'unable to do activity or extreme problems'.

For example, the health state, 11212, represents a patient who indicates no problems on mobility, self-care, and pain/discomfort (represented by 1s) but some problems on usual activities and anxiety/depression (represented by 2s).

A utility index can be computed from the EQ 5D-5L descriptive system with utility scores ranging from -0.281 (worst imaginable health state) to 1 (best imaginable health state), with -0.281 representing an "unconscious" health state.

The EQ-5D-5L index scores obtained from the directly elicited English value set based on

time-trade off (TTO) valuation technique will be used for summary statistics at any particular visit and for change from baseline calculation.

EQ-5D-5L English Value set

An excel file contains the EQ-5D-5L English value set. In the Excel file there are two spreadsheets: (1) 'Calculator' allows to enter the values from the EQ-5D-5L and can automatically calculate the index score; (2) 'English EQ-5D-5L index' provides a list of all the potential responses and corresponding index values. The English value set will be used to calculate the index scores for all patients enrolled in the study.

The excel file can be downloaded from the EuroQol Group website: https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation/. The reference publication is: ”Devlin N, Shah K, Feng Y, Mulhern B, van Hout B.Valuing Health-Related Quality of Life: An EQ-5D-5L Value Set for England. OHE Research Paper January 2016. London: Office of Health Economics; 2016.”

The data will be uploaded in the following Credi folder: Cabinets/CREDI Projects/S/SOM230C/CREDI Studies/SOM230C2413/Administrative Files (study level)/CIS (Clinical Information Sciences)/Biostatistics. The excel file will be called “CSOM230C_CSOM230C2413_ EuroQol_EQ-5D-5L_England_Value_Set.xls ”The excel file will be uploaded from the website and put in final state by the CTH before being uploaded to GPS. Once the excel file is in final state in Credi, the Trial Programmer will be responsible to upload the file into GPS via WDCS. The file will be uploaded with production status in the following folder: \SOM230C\SOM230C2413\util\. The excel file will keep the same name as in Credi.

A SAS dataset will then be created by the Trial Programmer based on the excel file to allow further programming tasks.

This excel file will be used to derive the EQ-5D-5L index scores for their dimension responses.

The EQ-5D VAS records the subject's self-rated health state on a 100-point vertical VAS (0=worst imaginable health state; 100=best imaginable health state). This information can be used as a quantitative measure of health outcome as judged by the individual respondents.

The details about the outputs and the reference EQ-5D-5L index using crosswalk value set will be provided in RAP M7.

17.9 Data handling conventions

Date imputation for AEs and concomitant medications will be imputed according to Novartis conventions described in [RAP Module 8].

For other date imputations and only for analysis purposes, the following imputation rules will be used to impute partial dates: if the day and month is missing, it will be replaced by 30th June (to be used only for events prior to study drug start date, e.g. medical history); if only the day is missing it will be replaced by the 15th of that month. For the dates known to be within the trial period, if this imputation makes the date later than the trial completion date, then the trial completion date is used; if the imputed date is earlier than the study drug start date, then the study drug start date is used.

Partial dates will remain partial in the data listings.

17.10 Other rules

Percentages in shift tables cross-tabulating baseline versus post-baseline values will be based on all patients with a non-missing post-baseline value in the respective analysis set.

17.11 Number of decimal places

Whenever possible, minimum and maximum will be presented to the same precision as the raw data. Mean and median will be presented to one more decimal place and standard deviation to two more decimal places.

Unless stated otherwise, no imputation for missing data will be performed.

17.12 SAS procedure used

The 100 × (1 – *alpha level*)% CI for the proportion of responders (binary outcome = 1 or

"Yes"), is obtained from the following:

PROC FREQ data = dataset;

TABLES binary event / binomial (ac wilson exact) alpha = alpha level;

WEIGHT count;

Run;

Reference: SAS Institute Inc. 2012. Base SAS® 9.3 Procedures Guide: Statistical Procedures, Second Edition. Cary, NC: SAS Institute Inc.

NOVARTIS

Clinical Development

CSOM230/Pasireotide

CSOM230C2413 / NCT02354508

A phase IIIb multicenter, open-label, single arm study to evaluate the efficacy and safety of pasireotide in patients with acromegaly inadequately controlled with first generation somatostatin analogues

Statistical Analysis Plan (SAP) : Extension Phase

Author: [redacted] Trial Statistician

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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
10-06-2018	Prior to DB lock	Creation of final version	N/A - First version	NA

Table of contents

List of abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
bid	bis in diem/twice a day
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
IVR	Interactive Voice Response
IWR	Interactive Web Response
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NCI	National Cancer Institute
o.d.	Once Daily
OS	Overall Survival
PFS	Progression-Free Survival
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
qd	Qua'que di'e / once a day
QoL	Quality of Life
RAP	Report and Analysis Process
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SOC	System Organ Class
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

The RAP module describes all the planned statistical methods for all safety and efficacy analysis using the core and extension phase data of CSOM230C2413 study. These analyses will be performed for the final CSR of the study.

Results from the primary analysis (primary endpoint and secondary endpoints for core phase) were described in the primary analysis CSR dated dd-Mmm-2018 with a data cut-off date of 08-Jan-2018 at which time all enrolled patients completed the core phase (i.e. patient completed the Week 36 visit) or discontinued earlier duirng this core phase of the trial.

The final CSR will focus on the analysis of long-term efficacy and safety in the subsequent extension phase of pasireotide LAR.

Unless otherwise specified, same analysis as in the RAP M3 of the core phase will be used.

Any changes made to the statistical plan and methodology after the clinical database lock will be documented separately. The statistical analysis of this study will be performed by Novartis personnel. A detailed description of the statistical analysis methods will be provided in Appendix 16.1.9 of the CSR.

Analysis data sets and statistical outputs will be produced using the most recent SAS® Version (SAS Institute Inc., Cary, NC, USA), and stored in Novartis global programming & statistical environment(GPS).

1.1 References

The following documents were used to develop the Statistical Analysis Plan.

- CSR template
- Protocol CSOM230C2413
- RAP M3 : Detailed Statistical Methodology of CSOM230C2413
- Protocol CSOM230C2402
- RAP M3: Detailed Statistical Methodology of CSOM230C2402
- Oncology guideline for safety analysis
- Annotated Case Report Form
- Report & Analysis Plan for Novartis Oncology
- Guidelines for content of Statistical Appendices of the Clinical Study Report

2 Study objectives and design

2.1 Study Objectives

See Section 2 of RAP M3 of the core phase CSR for the objectives pertaining to the core phase. The primary and secondary-core phase analyses were performed at the time of the primary analysis (at end of core phase) and reported in the respective CSR.

This SAP describes the planned continued efficacy and safety analyses pertaining to the extension phase of pasireotide LAR. Objectives and related endpoints for the extension phase are described below.

Objective	Endpoint
Secondary-extension phase	
To assess the proportion of patients achieving IGF-1 <ULN at weeks 48, 60 and 72	Proportion of patients who achieved IGF-1 <ULN at weeks 48, 60 and 72
To assess the proportion of patients achieving GH <1 µg/L and IGF-1 <ULN at weeks 48, 60 and 72 by treatment with pasireotide LAR alone or with concomitant medications used to treat acromegaly	Proportion of patients who achieved GH <1 µg/L and IGF-1 <ULN at weeks 48, 60 and 72 by treatment with pasireotide LAR alone or with concomitant medications used to treat acromegaly
To assess the proportion of patients achieving GH <1 µg/L at weeks 48, 60 and 72 by treatment with pasireotide LAR alone or with concomitant medications used to treat acromegaly	Proportion of patients who achieved GH <1 µg/L at weeks 48, 60 and 72 by treatment with pasireotide LAR alone or with concomitant medications used to treat acromegaly
To evaluate the long term tolerability and safety profile of pasireotide LAR	Toxicity will be assessed using the National Cancer Institute-Common Toxicology Criteria Adverse Events version 4 (NCI-CTCAE v.4.03) and for laboratory assessments that include biochemistry, hematology, urinalysis; special safety assessments that include the regular monitoring and recording of blood glucose, insulin, HbA1c, GH and IGF-1, thyroid and

	liver function tests, gallbladder examinations and ECGs. Concomitant medications/Significant nondrug therapies will be assessed from study enrollment until the safety follow-up.
To evaluate the long term effect of pasireotide LAR on HRQoL and signs and symptoms of acromegaly, from baseline and week 36 to week 72	Change in scores as measured by AcroQoL, EQ-5D- 5L and signs and symptoms of acromegaly from baseline to week 72 and from week 36 to week 72.

2.2 Study design and treatment

This is a phase IIIb exploratory study to assess the efficacy and safety of pasireotide in patients with acromegaly inadequately controlled with first generation somtostatin analogues.It is planned that the data from all centers that participate in this protocol will be used.

Study drug refers to pasireotide LAR (10mg, 20mg,40mg or 60mg). The brief description of the study design is given below :

Group 1 - Patients would be treated with octreotide LAR 30mg from the countries where octreotide LAR 40mg is approved for the treatment of acromegaly at the time of screening – Patients participate in the run-in phase.

Run-In phase (Screening to Baseline):

Patients would start treatment with octreotide LAR 40 mg every 4 weeks. Patients who have not achieved biochemical control after 3 injections can be enrolled in the study.

Core Phase (Baseline to week 36):

Patients would start treatment on pasireotide LAR 40 mg every 4 weeks until week 32. A mean GH value and IGF-1 value was assessed every 12 weeks until week 36. The dose could be adjusted after the evaluation of biochemical control. During the core phase any acromegaly concomitant medication was prohibited.

Extension Phase (week 36 to week 76):

Patients would receive the same dose of pasireotide LAR at week 36, which would be the first dose of study medication in the extension phase. At week 40 the dose could be adjusted and acromegaly concomitant medication could be added to the treatment if, patients remain uncontrolled. Patients would receive pasireotide LAR 40mg/60mg until week 68 for a total of 32 weeks in the extension phase. A mean GH value and IGF-1 value would be assessed every 12 weeks until week 72.

Safety follow-up:

After discontinuation or completion of study treatment, all patients would be followed for safety 12 weeks after the last study drug administration.

Group 2 – Patients who were treated with octreotide 30 mg from countries where octreotide 40mg has NOT been approved for the treatment of acromegaly at screening or patients treated with octreotide 40mg or lanreotide 120mg would not have the run-in phase.

Core Phase (Baseline to week 36):

Same procedure to be followed as Group 1.

Extension Phase (week 36 to week 76):

Same procedure to be followed as Group 1.

Safety follow-up:

Same procedure to be followed as Group 1.

3 Data included in the analysis

All data reported in the database (scheduled, repeat and unscheduled visits) up to the end of the study will be included in the final CSR.

Final analysis will be conducted when all patients complete the extension phase or have discontinued the study prior to completing the extension phase of the trial. The final analysis will be performed on all data that has been collected up to the final CSR DBL (generally 12 weeks after LPLV).

The final CSR will include:

- Analyses using data from both core and extension phase(wherever applicable)
- Extension phase specific results.

4 Statistical methods : Analysis sets

The definition of the analyses sets will remain same during the core and extension phase.

4.1 Full analysis set

The **Full Analysis Set (FAS)** comprises all patients who have signed informed consent and have been treated with at least one dose of study medication (pasireotide LAR) after enrollment into the study. The protocol states that the FAS comprises all patients to whom study treatment has been assigned. The definition of the FAS in the SAP specifies that with study treatment it is meant Pasireotide LAR to avoid confusion with the second treatment drug Octreotide LAR.

Extension Full Analysis Set (Extension FAS) would include all the patients who would recieve at least one dose of pasireotide LAR in the extension phase.

4.2 Safety set

The **Safety Set** includes all patients who received at least one dose of study medication (Pasireotide LAR) with a post-baseline safety assessment. The statement that a patient has no AE constitutes a safety assessment.

5 Patients and treatments

5.1.1 Patient disposition

The number of patients who completed or discontinued the extension phase of the study will be summarized using the extension full analysis set by the treatment group based on the dose of pasireotide monotherapy and combination treatment as defined the RAP M3 for core phase. The following summaries will be provided:

- Number (%) of patients who completed the core phase
- Number (%) of patients who entered extension phase
- Number (%) of patients who completed extension phase
- Number (%) of patients who discontinued and reason for discontinuation prior to week 72 (extension phase, visit 778) after completing the core phase.

5.1.2 Protocol Deviation Summaries

The number and percentage of patients in the extension FAS with any CSR reportable protocol deviation will be tabulated by the protocol deviation category. Listing will also be provided for all the protocol deviations based on extension FAS.

5.1.3 Background and demographic characteristics

All demographic and background data (e.g. age, gender, race) will be summarized and listed in the Extension FAS by treatment group.

Qualitative characteristics (e.g., gender) will be summarized by means of contingency tables. Quantitative variables (i.e., age, weight, BMI) will be summarized by appropriate descriptive statistics (i.e., mean, SD, median, minimum, maximum).

Baseline diabetic status, mean GH and IGF-1 at baseline will also be summarized for each treatment group.

Please refer to section 8.4 of RAP M7 of the core phase for the definition of the baseline diabetic status.

6 Study Drug

Study drug refers to pasireotide LAR (10 mg, 20 mg, 40 mg or 60 mg).

6.1 Study medication

The safety set and the extension safety set will be used for all summaries and listings of study medication.

Duration of exposure to study drug, number of injections taken and number of patients with dose change and/or dose delay along with reasons for dose change/dose delay, will be summarized by appropriate descriptive statistics. In addition, number of injections will be summarized categorically (categories to be specified in RAP Module 7).

All doses of the study drug along with reasons for dose change/delay will be listed.

The above summaries and listings will be provided for overall study period (core + extension phase) using the Safety set, and separately for extension phase using the Extension safety set.

6.2 Exposure

The following definitions will be used corresponding to study drug pasireotide LAR only:

For overall study period:

Study drug start date is defined as the first date when a non-zero dose of study drug (pasireotide LAR) was administered and recorded on the Drug Administration Record (DAR) CRF page.

Study drug end date is defined as the last date when a non-zero dose of study drug (pasireotide LAR) was administered in the study (either core or extension period depending on when the patient discontinued study drug).

Extension phase :

Study drug start date is defined as the first date when a non zero dose of study drug (pasireotide LAR) was administered during the extension phase and recorded on the Drug Administration Record (DAR) CRF page.

Study drug end date is defined as the last date when a non-zero dose of study drug (pasireotide LAR) was administered in the extension phase of the study.

Duration of exposure for overall study period (in weeks) will be calculated as:
{min(study drug end date + 27 days; death date) – study drug start date in core + 1 day} / 7 days.

Duration of exposure for overall study period (in months) will be calculated as:

{min(study drug end date + 27 days; death date) – study drug start date in core + 1 day} / 30.4375.

Cumulative dose (mg): total dose of study drug taken by a patient in the overall study period

Dose intensity (DI) (mg/month): cumulative dose (mg) / duration of exposure (months).

Note: The study drug end date for the overall study period could either be in core phase or extension phase depending on when the patient discontinued the study drug.

Duration of exposure in extension phase (in weeks) will be calculated as:
{min(study drug end date in extension phase + 27 days; death date) – study drug start date in extension phase + 1 day} / 7 days.

Duration of exposure extension phase (in months) will be calculated as:
{min(study drug end date in extension phase + 27 days; death date) – study drug start date in extension phase + 1 day} /30.4375

Cumulative dose (mg): total dose of study drug taken by a patient in the extension phase

DI (mg/month): cumulative dose (mg) / duration of exposure (months).

The duration includes periods of temporary interruption for any reason.

Duration of exposure will be presented overall and for up-titrated Pasireotide LAR 60 mg (highest dose received during the trial.)

7 Prior and concomitant medication

Prior and concomitant therapy is defined as all interventions (therapeutic treatments and procedures) besides the study treatment that are administered to a patient preceding or coinciding with the study assessment period.

Prior and concomitant medications and significant non-drug therapies for acromegaly and excluding acromegaly will be listed and summarized separately in the safety set and extension safety set.

The concomitant medications and significant non-drug therapies (for acromegaly and excluding acromegaly) will be provided for overall study period (core + extension phase) and separately for extension phase.

Separate summaries on prior and concomitant anti-diabetic medication after start of study drug (pasireotide LAR) will be provided for over study period and separately for extension phase.

Medications will be classified as prior or concomitant based on the following rules and will be coded using the WHO Drug Reference List to allow for categorization by preferred term:

- Prior medication are medications that started before the first dose of study drug regardless of whether the medication ended before or after the first dose of study drug.
- Concomitant medications are the medications that started on or after the first dose of study drug and continued after the first dose of study drug

In addition to categorizing medication data by preferred term, drugs will be classified according to their ATC classification in order to present and compare how they are being utilized. The ATC classification allows summarization of medications by a high-level common drug class.

Same summaries will be provided as in Section 10 of RAP M7 for the core phase analysis will be repeated for overall study period (core+extension phase) using the safety set and the extension phase using the extension safety set separately.

A separate listing will be provided for patients who take concomitant medication related to prolonging the QT interval and therefore at the risk of ventricular arrhythmia, Torsades de Pointes and sudden death for the overall study period (core + extension phase). The listing will only include the concomitant medications (with dose unit and frequency route) related to QT prolongation taken at the time of QT prolongation along with the ECG intervals. The patients who have > 60 ms QTcF change from baseline or QTcF > 480 ms will be flagged.

8 Medications known to affect GH and IGF-1 levels

During the core phase any acromegaly concomitant medication was prohibited. Medication taken in core phase (other than study drug) and known to affect GH and IGF-1 levels were identified as major protocol deviations.

Medications known to affect GH or IGF-1 levels will be allowed during the extension phase (starting from week 40) for patients who do not achieve biomedical control in the core phase.

The following concomitant medications will be used to treat acromegaly (WHO dictionary code in brackets):

- Somatostatin analogs (H01CB)
- Dopamine agonists (N04BC)
- Growth hormone receptor antagonists (H01AX)

In the extension phase, if there are more than 10 patients who take concomitant medications known to affect GH or IGF-1 levels, a summary table will be provided for those patients with medication data. If not, then only a listing will be provided.

9 Analysis of efficacy endpoints

9.1 Analyses time points

The analysis timepoint will be at week 72 of the extension phase as well as other scheduled visits of the extension phase

9.1.1 Graphical presentation of results

Plots for mean (+/- SE) of 5-point mean GH and standardized IGF-1 by visit will be provided for the extension period.

9.1.2 Handling missing values/censoring/discontinuations

If a patient has less than three samples for the assessment of the 5-point mean GH from the 2-hour profile, then the mean GH will be considered as missing. In addition, if GH and IGF-1 measurements are taken after 35 days from the date of any injection of study drug (from the scheduled dose date), the values will be considered as missing (the rationale has been adopted based on study CSOM230C2402). For a patient with missing values of mean GH or IGF-1 at 72 weeks or who withdraws earlier from the study will be considered as a non-responder.

9.2 Efficacy evaluation

The secondary efficacy analyses will be performed on the extension FAS. The same rule of handling missing values for GH and IGF-1 variables as specified in the analyses of the primary efficacy variable will be used same as in Section 13.2 of RAP M7 of the core phase.

9.2.1 Secondary objectives – Extension phase

9.2.1.1 To assess the proportion of patients achieving IGF-1 < ULN atweeks 48, 60 and 72 by treatment with pasireotide LAR alone or with concomitant medications used to treat acromegaly

Proportion of patients who achieved IGF-1 < ULN by treatment with pasireotide LAR alone or with concomitant medications used to treat acromegaly will be reported separately (if there are 10 more patients with concomitant medications used to treat acromegaly in extension phase) along with its two-sided 95% confidence interval at week 48, 60 and 72.

9.2.1.2 To assess the proportion of patients achieving GH < 1 µg/L and IGF-1 < ULN at weeks 48, 60 and 72 by treatment with pasireotide LAR alone or with concomitant medications used to treat acromegaly

Proportion of patients who achieved GH < 1 µg/L and IGF-1 < ULN by treatment with pasireotide LAR alone or with concomitant medications used to treat acromegaly will be reported separately (if there are 10 more patients with concomitant medications used to treat acromegaly in extension phase) along with its corresponding 95% confidence interval at weeks 48, 60 and 72.

9.2.1.3 To assess the proportion of patients achieving GH < 1 µg/L at weeks 48, 60 and 72 by treatment with pasireotide LAR alone or with concomitant medications used to treat acromegaly

Proportion of patients who achieved GH < 1 µg/L by treatment with pasireotide LAR alone or with concomitant medications used to treat acromegaly will be reported separately (if there are 10 more patients with concomitant medications used to treat acromegaly in extension phase) along with its corresponding 95% confidence interval at weeks 48, 60 and 72.

9.2.1.4 To evaluate the long term effect of pasireotide LAR on HRQoL, EQ-5D-5L and signs and symptoms of acromegaly, from baseline and week 36 to week 72

Descriptive statistics, including mean, median, standard deviation, minimum and maximum, will be presented for all patient-reported outcomes (PRO) to describe actual standardized scores as measured by HRQoL and EQ-5D-5L index scores and EQ-VAS scores. For each acromegaly symptoms (ring size, headache, fatigue, perspiration, paresthesias, osteoarthralgia), descriptive summaries of actual and changes will be provided.

For each of the PRO variables (AcroQoL score (total score, physical sub-score and psychological sub-score [psychological/physical appearance and psychological/personal relations]), EQ-5D-5L utility index and EQ-5D-5L VAS score):

- Change in PRO scores from
    - baseline to week 72
    - week 36 to week 72

For the self-reported signs and symptoms (ring size, headache, fatigue, perspiration, paresthesias, osteoarthralgia):

- Change in symptom severity scores (for each sign and symptom) from
    - baseline to week 72
    - week 36 to week 72
- Shift tables from baseline to most extreme post-baseline value up to week 72 will also be presented for acromegaly symptoms except ring size.

9.2.2 Graphical presentation of results

Plot of mean values of AcroQoL score by visit (total score, physical sub-score and psychological sub-score [psychological/physical appearance and psychological/personal relations]), EQ-5D-5L (utility index and VAS score) by visit will be provided. A multiple bar chart corresponding to proportion of patients to each response categories for the EQ-5D dimension will be provided (layout will be specified in RAP Module 7). The plots will be considered for the extension period only.

10 Statistical methods for safety analysis

Safety assessments will consist of monitoring and recording all adverse events (AEs), including serious adverse events (SAEs), the regular monitoring of hematology (including coagulation parameters), blood chemistry (including fasting blood glucose), glycosylated hemoglobin, fasting serum cortisol, plasma adrenocorticotropic hormone, liver and thyroid function tests, urinalysis, injection site reactions, physical examinations including vital signs, gallbladder ultrasound, ECGs and body weight.

All the safety analysis will be based on safety set and extension safety set (as applicable).

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

1. pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
2. on-treatment period: from day of first dose of study medication to 84 days after last dose of study medication
3. post-treatment period: starting at day 84 days + 1 after last dose of study medication

For the overall study period and extension phase, all listings and tables will be presented overall, by maximum dose and by type of treatment (monotherapy, combination dopamine agonist, and combination with GH receptor antagonist). For AESIs tables will be presented by the given dose as well (AE starts or worsens while the patient is being treated at that dose level).

10.1 Adverse Events

10.1.1 Coding of AEs

All adverse events will be coded using the latest MedDRA coding dictionary that provides the system organ class and preferred term information available during the time of required analyses.

10.1.2 Grading of AEs

Adverse events will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

10.1.3 General rules for AE reporting

Summary tables for adverse events (AEs) from the study will include AEs that started or worsened in the period from study drug start date up to the patient's last day on the study (inclusive), but no later than 84 days after study drug end date. The incidence of treatment-emergent AEs (new or worsening from baseline) will be summarized by SOC and/or PT, severity (based on CTCAE grades), type of AE and relation to study treatment. If an AE deteriorates or improves over time, new event will be reported accordingly with new severity.

Deaths will be listed and summarized by cause of death.

10.1.4 AE summaries

Adverse events will be summarized and listed in the following way:

- AEs, regardless of study drug relationship
- AEs, suspected to be study drug related
- SAEs, regardless of study drug relationship
- SAEs, suspected to be study drug related
- AEs leading to discontinuation/dose adjustment or interruption/additional therapy
- AEs of special interest
- Deaths by primary system organ class and preferred term
- Hyperglycemia-related AEs by diabetic status at baseline, by preferred term and maximum CTC grade

Adverse events will be presented overall and for up-titrated Pasireotide LAR 60 mg (highest dose received during the trial).

The presentation of the adverse events summary based on SOC, PT, maximum grade will be specified in appropriate layouts in RAP Module 7.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment-emergent adverse events which are not serious adverse events with an incidence greater than 5% and on treatment-emergent 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.

10.1.5 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.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 (in [Cabinets/CREDI Projects/S/SOM230C/Administrative files/CIS (Clinical Information Sciences)/Biostatistics/SOM230C_AESI_MedDRA xx x<use the latest available version>_ddMMMyyyy.xls<use the latest available data set>]) will be used.

The following summary will include the following:

- AESI, regardless of study drug relationship, with maximum grade, suspected to be study drug related, SAEs, leading to discontinuation and requiring dose adjustments

10.2 Laboratory values

The severity grades for laboratory values are derived using NCI/NIH Common Toxicity Criteria (CTC). A severity grade of zero will be assigned when the value is within normal limits. All laboratory values will be converted into SI units. However, blood glucose will also be presented in mg/dL and assessed using the ADA criteria 2010.

The following laboratory parameters will be collected:

Test category	Test name
Hematology (central)	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, RBC Morphology with differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)
Clinical Chemistry (central)	Bicarbonate, Calcium, Chloride, Creatinine*, Creatine Kinase, Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, α-amylase, Lipase, Lactic Dehydrogenase (LDH), Magnesium, Sodium, Potassium, Prolactin
Liver Function Tests (Central)	ALT, AST, Total bilirubin (total bilirubin should be differentiated into direct and indirect reacting bilirubin if total bilirubin is increased > 2 × ULN), Albumin, ALP and GGT
Hepatic Screening (Central)	HbsAg, AntiHCV
Hyperglycemia related test (Central)	Fasting blood glucose, Glycosylated Hemoglobin (HbA1C), oGTT (insulin and plasma glucose)
Coagulation (central)	Prothrombin time (PT) or International normalized ratio (NR), Partial thromboplastin
Thyroid and hormones (central)	T4 [free], TSH, Plasma Adrenocorticotropic Hormone (ACTH), Fasting Serum Cortisol
Urinalysis (local)	Macroscopic Panel (Dipstick) (Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, pH,
Additional tests (central)	Insulin-like growth factor 1 (IGF-1), Growth Hormone (GH)
Pregnancy test	Urine (dipstick) and serum B-hCG

(*) Q2 Serum Creatinine Issue

An equipment malfunction issue was identified with respect to one of the Beckman Coulter AU5400 units in the Valencia Laboratory. Serum Creatinine samples analyzed between 01-Oct-2016 to 13-Jan-2017 were impacted. Sample results that could not be repeated for this study (because there was no backup sample) will be annotated in the clinical data base as reported but unreliable and therefore will be considered unreliable. Data will remain in the clinical data base, but will not be used as part of CSR statistical analyses. These unreliable results will appear in the listings, but they will be excluded from the biochemistry shift table analyses. Results obtained which were repeated and confirmed within 10% of the original samples will be used for statistical analyses and listed. Results obtained that were repeated and not within 10% of the original samples will be replaced in the clinical data base by the retest values and will be used for statistical analyses and listed.

Summaries for laboratory parameters will include all laboratory assessments collected in the core and extension phase.

For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used. In the unlikely case when a local laboratory normal range overlaps into the higher (i.e. non-zero) CTC grade, the laboratory value will still be taken as within normal limits and assigned a CTC grade of zero. 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.

The following summaries will be produced for the laboratory data (by laboratory parameter) corresponding to on-treatment period for post-baseline values:

- Shift tables using CTCAE grades to compare baseline/extension baseline to the worst on-treatment value,
- For laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high classification to compare baseline/extension baseline to the worst on-treatment value,
- Number and percentage of patients meeting individual and composite Hy's Law criteria (i.e. ALT > 3 × ULN with concurrent total bilirubin >2 × ULN, without increases in alkaline phosphatase and no other cause(s) identified for the abnormal findings) for liver injury (each patient will be counted only for the worst observed post baseline/post extension baseline value),
- Fasting blood glucose (FBG) [< 100 mg/dL, ≥ 100 - < 126 mg/dL and ≥ 126 mg/dL] using the ADA (2010) classifications to compare baseline/extension baseline to last on-treatment value.
- For the shift tables for blood glucose (HbA1C) cut-offs similar to the ADA (2010) will be used, defined as (<5.7%, >=5.7% - <6.5%, >=6.5 - <8% and >=8%) to compare baseline/extension baseline to the last on-treatment value,

The following listings will be produced for the laboratory data:

- Listings of patients with laboratory values outside the laboratory reference ranges with values flagged to show the corresponding CTCAE grades and the classification relative to the laboratory reference ranges.
- Listings of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges,
- Listing of patients with notable laboratory abnormalities (i.e., newly occurring CTCAE grade 3 or 4 laboratory toxicities).

10.2.1 Graphical presentation of results

Plots for mean (+/- SE) of FBG and HbA1c by visit will be provided for the extension phase and overall study period (core + extension phase).

10.3 Vital signs and weight

Vital signs (blood pressure, heart rate and body temperature) and weight will be summarized and listed by visit and treatment group. Patients with clinically notable vital sign values will be flagged in the listing. The summaries will be provided for overall study period and for extension phase.
The criteria for clinically notable values remains same as described in the core SAP.

The following summaries will be produced for each vital sign parameter:

- Vital signs shift table based on notable values

10.4 ECG

The following analyses will be performed for VR, PR, QT intervals and QRS duration, ventricular rate, and QTcF (Fridericia's formula) during the on- treatment period:

- Summary statistics at baseline/extension baseline and all scheduled post-baseline/post extension baseline time points,
- Summary statistics of changes from baseline/extension baseline at each scheduled post-baseline/post-extension baseline time point,
- Listing of ECG data (scheduled and unscheduled visits).

Number (%) of patients with a notable and newly occurring QT interval, based on QTcF will be summarized. ECG shift table based on notable values from baseline/extension baseline to worst post-baseline/post-extension baseline value will be summarized. The notable criteria for QT/QTcF, PR, VR and QRS will remain same as described in the core SAP. :

A patient with multiple occurrences of a notable QT interval or a newly occurring ECG abnormality is counted only once in that category.

Patients with notable QT interval values and newly occurring qualitative ECG abnormalities will be flagged in the listings.

No imputation of missing data will be performed.

The formula used to calculate the QT interval crrected for heart rate is :

- Fridericia's formula, $QTcF = QT/\sqrt[3]{RR}$

10.5 Gallbladder ultrasound

Gallbladder data at each visit will be summarized and listed by treatment group. Shifts from baseline/extension baseline to last post-baseline/post-extension baseline value will be presented for each individual item.

11 Appendix 16.1.7 Randomization scheme and codes

Not applicable for the extension phase.

12 Appendix 16.1.9 Documentation of statistical methods

This section of the RAP document presents further detail about the statistical methods not given in Section 9.7 of the Clinical Study Report (CSR).

12.1 Extension baseline definition

The extension baseline is defined as the last available value (or assessment) prior to the dose of pasireotide LAR in the extension phase (i.e., prior to Visit 18 or week 36) . The extension baseline definition is only applicable for patients who moved in the extension phase.

- For Fasting glucose, HbA1c, Gallbladder, ECG, biochemistry, hematology, vital signs and liver, Extension baseline will be the last available value **on or before** the first injection date of the extension phase.
- For patients **having anti-diabetic** intervention at extension baseline is considered, if patients has taken **at least one antidiabetic** medication (ATCCODE = ‘A10’) **before** the first injection in the extension phase.