CSOM230B2412

An open label, multi-center pasireotide roll-over study for patients who have completed a previous Novartis-sponsored pasireotide study and are judged by the investigator to benefit from continued pasireotide treatment

Statistical Analysis Plan

Version	2
Date	15 March 2024
Total Page Number	28
Attachment	2

Revision History

Date	Version	Summary of Changes
20 April 2017	1.0	First Version
29 June 2017	1.0	Incorporated comments from LS, clinical team and statistical programming team
6 September 2019	Amendment 1	Addition of new parent studies to Table 2-1
9 February 2021	1.1	Change of sponsor Reformatting according with SOP 06BM13R02
29 September 2023	1.2	Revision for final study report
13 October 2023	1.3	Correction of cut-off percentage for AEs tables
15 March 2024	2.0	Update because of discrepancies identified during the the audit on Clinical Study Report - Alignement with protocol amendment 5 - End of study definition

Approval Page

Document Title: **An open label, multi-center pasireotide roll-over study for patients who have completed a previous Novartis- sponsored pasireotide study and are judged by the investigator to benefit from continued pasireotide treatment**
Version 2.0

Prepared and approved by:

Name (Title)	**Signature**	**Date**
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Effective Date: 15 March 2024

Contents

1 LIST OF ABBREVIATIONS

AE	Adverse event
AESI	Adverse Event of Special Interest
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DI	Dose Intensity
FAS	Full Analysis Set
EC	Ethic Committee
eCRF	Electronic Case Report Form
EOT	End Of Treatment
IIT	Investigator Initiated Trial
IRB	Institutional Review Board
LAR	Long Active Release
MedDRA	Medical Dictionary for Drug Regulatory Affairs
PASS	Post Authorization Safety Study
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
s.c.	Sub-cutaneous
SOC	System Organ Class

2 INTRODUCTION

This statistical analysis plan (SAP) describes all planned analyses for the clinical study report (CSR) of study CSOM230B2412, an open-label, multi-center, Phase IV, roll-over study in patients who have completed a prior Novartis-sponsored pasireotide (SOM230) study and are judged by the investigator to benefit from continued treatment with pasireotide.
The content of this SAP is based on protocol CSOM230B2412 Amendment 5.0. All decisions regarding final analysis, as defined in the SAP document, will be made prior to database lock.

2.1 CLINICAL OBJECTIVES

The purpose of the study is to evaluate the long-term safety.

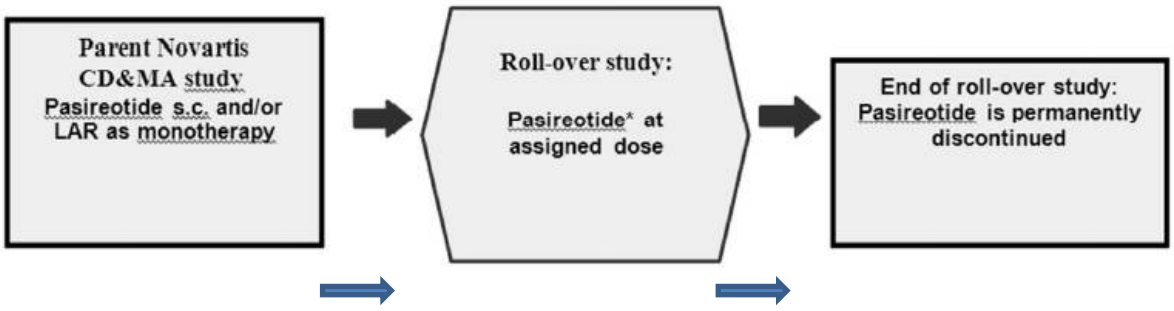
2.2 STATISTICAL DESIGN / MODEL

This is a multi-center, open label, phase IV, roll-over study of pasireotide in patients being treated in previous Novartis Oncology-sponsored studies and who are benefiting from treatment with pasireotide by their parent study investigator. The parent studies that are eligible to participate in the roll-over study were decided by Novartis. Investigator initiated trials (IIT) will not be included.

There will be no screening period for this study. At the enrollment visit, the patient will be consented to the study and eligible patients can start their treatment with pasireotide. Patients must return to the clinic at any given time as per standard of care, however only four study visits per year (with the exception of 5 visits within the first year) will be recorded for patients receiving pasireotide s.c. and monthly visits for those patients receiving pasireotide LAR.
All adverse events and serious adverse events will be collected continuously throughout the study.

At every visit, the investigator is required to confirm that the patient continues to have clinical benefit and may continue receiving study treatment.
Study design is described in Figure 2-1 below.

Figure 2-1 Study Design



*Note: The starting dose of pasireotide should be the same dose as that which the patient was receiving in the parent study at roll over.

2.3 Timing of interim analyses and design adaptations

This study has also been categorized as voluntary European Post Authorization Safety Study (PASS). Therefore, regular interim analyses will be performed during the course of the study. Interim analyses will be performed as need by the Sponsor and approximately at the following time points:

- Q4 2017
- Q4 2019
- Q4 2021
- Q4 2023

2.4 Definition of end of the study

End of study is defined as either 10 years from FPFV (or until 10-Jun-2023 in the UK) or when all patients on this study have permanently discontinued pasireotide treatment or have been able to obtain commercial supply according to local regulations or have been able to receive the drug through country-specific programmes outside of this clinical trial (applicable to Brazil, France, Germany, India, Italy, Malaysia, Mexico, Peru and Thailand) and the end of treatment visit and all safety follow-up procedures have been performed for each patient, whichever comes first.

2.5 Early study termination

The study can be terminated at any time for any reason by Recordati. Should this be necessary, the patient should be informed as soon as possible and should stop taking study labeled drug. Assessments should be performed as described in Protocol Section 7.1.3 for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

2.6 STATISTICAL SOFTWARE

SAS version 9.4 or higher will be used in all analyses.

3 CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Not applicable.

4 STATISTICAL METHODS

This section contains information that will be used to draft CSR Section 9.7 on statistical analysis.

4.1 Data analysis general information

The statistical analysis of these data will be performed by IQVIA personnel in accordance with the data analysis section, Section 10, of the study protocol which is available in [Appendix 16.1.1 of the CSR]. Important information is given in the following sections and details are provided, as applicable, in [Appendix 16.1.9 of the CSR].

Data included in the analysis

Final analyses will be performed when all patients have been followed for 3 months (84 days) following the last dose of pasireotide LAR treatment and for 1 month (30 days) following the last dose of pasireotide s.c. treatment.

All events with start date before or on the cut-off date and end date after the cut-off date will be reported as 'continuing at the cut-off date'. The same rule will be applied to events starting before or on the cut-off date and not having documented end date. This approach applies, in particular, to adverse event reports. For these events, the end date will not be imputed and therefore will not appear in the listings.

It is planned that the data from all centers that participate in this trial will be pooled and analyzed. Unless otherwise specified, qualitative data will be described using frequency and percentages, while quantitative data, will be described using descriptive statistics: n, mean, standard deviation, median, minimum, and maximum.

All data will be summarized and listed by indication (acromegaly, Cushing's disease and Others) and formulation (s.c. and LAR).

For the formulation, the variable can be derived from the DAR panel from the DARTYP1C variable, the values captured are 533 and 838 which correspond to Pasireotide LAR and Pasireotide s.c., respectively.

The indication will be derived based upon the parent study number from the HIS panel using the PRVSTY2C variable as described in the following Table 2-1 with the exception of parent study numbers CSOM230C2110E and CSOM230B2219. For those two parent studies, the indication will be derived from the parent study data sets as shown in Table 2-2.

Table 2-1 Derivation of the indication information – Part 1

Parent study number	eCRF	Indication	Indication group
CSOM230B2201E	78	Acromegaly	Acromegaly
CSOM230B2208E	79	Cushing's disease	Cushing's disease
CSOM230D2203	81	NET other pituitary and EAS	Other diseases
CSOM230B2305	82	Cushing's disease	Cushing's disease
CSOM230X2203	83	Dumping syndrome	Other diseases
CSOM230C2305	84	Acromegaly	Acromegaly
CSOM230G2304	85	Cushing's disease	Cushing's disease
CSOM230C1202	86	Acromegaly or pituitary	Acromegaly
CSOM230C2402	87	Acromegaly	Acromegaly
CSOM230X2404	115	Melanoma	Other diseases
CSOM230X2404	116	Melanoma	Other diseases
CSOM230C2413	117	Acromegaly	Acromegaly
CSOM230B2411	125	Cushing's disease	Cushing's disease
CSOM230XDE04	126	Prostate cancer	Other diseases
CSOM230D2401	136	Pituitary adenomas	Other diseases
CSOM230DIC03	137	NET	Other diseases

Table 2-2 Derivation of the indication information – Part 2

Parent study number	eCRF code	Parent data set	Parent data set variable	Indication	Indication group
CSOM230C2110E1	80	ADMG	CLIND	Carcinoid	Other diseases
CSOM230C2110E1	80	ADMG	CLIND	Acromegaly	Acromegaly
CSOM230B2219	114 or 113	AIDENT	DISTYP3A	Acromegaly	Acromegaly
CSOM230B2219	114 or 113	AIDENT	DISTYP3A	Cushing's disease	Cushing's disease

Treatment period

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

on-treatment period: from day of first dose of study medication in the roll-over study to 3 months (84 days) following the last dose of pasireotide LAR treatment and to 1 month (30 days) following the last dose of pasireotide s.c. treatment.

post-treatment period: starting at 3 months+1 day (day 85) following the last dose of pasireotide LAR treatment and at 1 month+1 day (day 31) following the last dose of pasireotide s.c. treatment.

Safety summaries (tables, figures) include only data from the on-treatment period. In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

However, all safety data (including those from the post-treatment period) will be listed and those collected during the post-treatment period will be flagged.

Study Treatment

Study drug and investigational treatment refer to pasireotide. Patients are to use the study treatment based on the parent protocol.

Date of first/last administration of study drug

The start date of study drug is defined as the first date when a non-zero dose of study drug was administered in the roll-over study and recorded on the Dosage Administration Record (DAR) eCRF.

The date of last administration of study drug is defined as the last date when a non-zero dose of study drug was administered and recorded on DAR eCRF.

Laboratory data

Pregnancy tests will be listed overall and by indication and formulation.

4.2 Patient disposition, demographics and other baseline characteristics

4.2.1 Patient disposition

Patient disposition will be summarized overall and by indication and formulation using the Safety Set. The number (%) of treated patients included in the Safety Set will be presented. The number (%) of patients in the Safety Set who are still on treatment, who discontinued the study treatment and the reason for discontinuation will be presented overall

The following summaries will be provided (with % based on the total number of Safety Set patients):

- Number (%) of patients who are still on-treatment at the time of data cut-off or final data base lock;
- Number (%) of patients who discontinued the study treatment;
- Number (%) of patients with primary reason for end of study treatment (based on patient status entered in the 'Study phase completion' page);

- Number (%) of patients who have entered the post-treatment follow-up safety evaluation (based on the 'Study completion' page);
- Number (%) of patients who have discontinued from the post-treatment follow-up (based on the 'Study Completion' page);
- Number (%) of patients with primary reason for end of study (based on patient status entered in the 'Study completion' page);

Listings will be provided overall and by indication and formulation for disposition, informed consent, inclusion/exclusion criteria using the Safety set.

4.2.2 Patient demographics and other baseline characteristics

Demographic information will be summarized and listed overall and by indication and formulation using the Safety Set. Demographic summary will include age and gender.

Categorical data (e.g. gender, age groups: 18 to <65 years, and ≥65 years) will be summarized by frequency counts and percentages. Continuous data (e.g. age) will be summarized by descriptive statistics (N, mean, median, standard deviation, minimum and maximum, 25th and 75th percentiles).

Demographic listing will include country, center, current patient ID, age and gender.

Medical history and ongoing medical conditions, including disease-related conditions and symptoms entered on (e) CRF will be summarized and listed overall and by indication and formulation. Separate summaries will be presented for ongoing and historical medical conditions. The summaries will be presented by primary system organ class (SOC) and preferred term (PT). Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

A listing of parent study history (parent study number, parent patient ID, parent study indication and parent study formulation) will also be provided using the Safety Set.

4.3 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

4.3.1 Study treatment / compliance

Dose administration data will be summarized overall and by indication and formulation using the Safety Set.

5 VARIABLES AND ENDPOINTS

Objectives and related endpoints are described in Table 5-1 below altogether with the planned analysis of collected data.

Table 5-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		
To evaluate long term safety data, i.e. SAEs and AEs	Frequency and severity of AEs/SAEs	The assessment of safety will be based on the frequency and severity of adverse events (AEs) and serious adverse events (SAEs)
Secondary		
To evaluate clinical benefit as assessed by the investigator	Proportion of patients with clinical benefit as assessed by the investigator at scheduled visits	Proportion of patients with clinical benefit as assessed by the investigator will be summarized at scheduled visits
Other secondary		
Not applicable	Not applicable	Not applicable

5.1 HANDLING OF MISSING DATA AND OUTLIERS

5.1.1 Study drug

Below mentioned imputation rules will be used in case of missing or partial end date of study drug.

Scenario 1

If the last date of study drug is after the cut-off date or is completely missing and there is no end of treatment eCRF page and no death date the patient should be considered to be on-going and use the cutoff date for the analysis as the last dosing date

Scenario 2

If the last date of study drug is completely or partially missing and there is EITHER an end of treatment eCRF page OR a death date available then imputed last dose date:

- = 31DECYYYY, if only Year is available and Year < Year of min (EOT visit date, death date)
- = Last day of the month, if both Year and Month are available and Year = Year of min (EOT visit date, death date) and Month < the month of min (EOT visit date, death date)
- = min (EOT visit date, death date), for all other cases

The imputed date will be compared with start date of study drug.

If the imputed date < start date of study drug, then last date of study drug is set to start date of study drug; otherwise, use the imputed date.

5.1.2 AE date imputation

Date imputation is the creation of a new, complete date from a partial one according to an agreed and acceptable algorithm. Missing date for AE will be handled according to rules

specified below. A partial date is simply an incomplete date e.g. DDOCT2001: the days are missing from this DDMMMYYYY date.

Partial AE start dates, if left partial, would ultimately mean the following:

It would not be possible to place the AE in time. Therefore the treatment/dosage at the time of the event would be unknown. So the event could not be reported/summarized appropriately – if at all.

Therefore it is important to perform date imputation to ensure that as many data events are represented as correctly as possible. Of course partial and/or missing dates should also be caught as edit checks and passed back to the investigator for resolution.

There **will be no** attempt to impute the following:

- **Missing** AE start dates
- AE start dates **missing the year**
- Partial/missing AE **end dates**

Table 5-1 AE/Treatment date abbreviations

	Day	Month	Year
Partial AE start date	<not used>	AEM	AEY
Treatment start date (TRTSTD)	<not used>	TRTM	TRTY

The following matrix Table 5-3 describes the possible combinations and their associated imputations. In the light grey boxes the upper text indicates the imputation and the lower text the relationship of the AE start date to the treatment start date (TRTSTD).

Table 5-2 AE partial date imputation algorithm

	AEM Missing	AEM < TRTM	AEM = TRTM	AEM > TRTM
AEY Missing	NC	NC	NC	NC
AEY < TRTY	Before TRTSTD (D)	Before TRTSTD (C)	Before TRTSTD (C)	Before TRTSTD (C)
AEY = TRTY	Uncertain (B)	Before TRTSTD (C)	Uncertain (B)	After TRTSTD (A)
AEY > TRTY	After TRTSTD (E)	After TRTSTD (A)	After TRTSTD (A)	After TRTSTD (A)

Table 5-3 AE/treatment date relationship and imputation legend

Relationship	
Before TRTSTD	Indicates AE start date prior to Treatment Start Date
After TRTSTD	Indicates AE start date after Treatment Start Date
Uncertain	Insufficient to determine the relationship of AE start date to Treatment Start Date

Imputation Calculation	
NC/Blank	No convention/imputation
(A)	01MONYYYY
(B)	TRTSTD+1
(C)	15MONYYYY
(D)	01JULYYYY
(E)	01JANYYYY

The following Table 5-5 gives a few examples.

Table 5-4 AE imputation example scenarios

Partial AE start date	Treatment start date	Relationship	Imputation calculation	Imputed date
12mmyyyy	20OCT2001	Uncertain	NC	<blank>
ddmmm2000	20OCT2001	Before	(D)	01JUL2000
ddmmm2002	20OCT2001	After	(E)	01JAN2002
ddmmm2001	20OCT2001	Uncertain	(B)	21OCT2001
ddSEP2001	20OCT2001	Before	(C)	15SEP2001
ddOCT2001	20OCT2001	Uncertain	(B)	21OCT2001
ddNOV2001	20OCT2001	After	(A)	01NOV2001

Any AEs with partial/missing dates will be displayed as such in the data listings.

Any AEs which are continuing as per data cut-off will be shown as 'ongoing' rather than the end date provided.

Incomplete date for death

All dates must be completed with day, month and year.

If the day or month is missing, death will be imputed to the maximum of the last contact date (excluding the date of death) and the following:

- Missing day: 15th of the month and year of death
- Missing day and month: July 1st of the year of death

5.2 DERIVATION RULES

5.2.1 AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

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

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected through the EOT eCRF page

5.2.2 Study day

Definitions will be applied for all situations:

- Study day for post-treatment event = event date – first dose date + 1
- Study day for pre-treatment event = first dose date - event date

The first day of study drug is study day 1.

If duration is to be reported in weeks, duration in days will be divided by 7, likewise if in months, then duration in days will be divided by 30.4375 and if in years, duration in days will be divided by 365.25.

6 ANALYSIS POPULATIONS

6.1 RELEVANT PROTOCOL DEVIATIONS

Protocol deviations will be categorized and tabulated overall and by indication and formulation into the following categories per ICH guidelines for CSR-reportable protocol deviations:

- Patient developed study/treatment withdrawal criteria during the study, but was not withdrawn
- Patient received the wrong treatment or incorrect dose
- Patient took an excluded concomitant medication
- Patient did not satisfy the entry criteria

Other important deviations may also be identified and summarized, as necessary, which may impact the scientific value of the trial.

The main protocol deviations are listed in Attachment 8.1. Additional terms can be identified on the basis of the collected data during study.

All protocol deviations will be listed overall and by indication and formulation using Safety Set.

6.2 DEFINITION OF POPULATIONS FOR ANALYSIS

6.2.1 Full Analysis Set

Not applicable.

6.2.2 Safety Set

The Safety Set includes all patients who received at least one dose of study medication (Pasireotide) after enrolling into the roll-over protocol.

6.2.3 Subgroup of interest

Not Applicable

7 PLANNED ANALYSES

7.1 Analysis of the primary objective

The primary objective is to evaluate long term safety as assessed by the occurrence of AEs / SAEs.

7.1.1 Primary endpoint

The assessment of safety will be based mainly on the frequency and severity of AEs, AESI and SAEs. See also Section 7.4.1.

7.1.2 Statistical hypothesis, model, and method of analysis

The primary endpoint will be summarized descriptively overall and by indication and formulation and no formal analysis will be performed. No hypothesis will be tested.

7.2 Analysis of secondary efficacy objective(s)

The secondary objective of the study is to evaluate clinical benefit as assessed by the investigator.

7.2.1 Secondary endpoints

Proportion of patients with clinical benefit as assessed by the investigator will be summarized at scheduled visits. Clinical benefit will be summarized overall and by indication and formulation using the Safety Set.

7.3 EXTENT OF EXPOSURE

Definitions of duration of exposure, cumulative dose, average daily dose, actual dose intensity (DI), as well as intermediate calculations, include:

Pasireotide s.c.:

- Duration of exposure (days): min(last date of rollover study drug, date of death, date of data cut-off) − first date of rollover study drug + 1
- Cumulative dose (µg): total dose of study drug taken by a patient in the rollover study
- Number of dosing days (days): duration of exposure − number of zero dose days
- Average daily dose (µg/day): cumulative dose (µg) / number of dosing days (days)
- DI (µg/day): cumulative dose (µg) / duration of exposure (days)

Pasireotide LAR:

- Duration of exposure (months): (min(last date of rollover study drug+27, date of death, date of data cut-off) − first date of rollover study drug + 1)/30.4375
- Cumulative dose (mg): total dose of study drug taken by a patient in the rollover study

- Number of dosing months (months): duration of exposure – number of zero dose months
- Average monthly dose (mg/month): cumulative dose (mg) / number of dosing months (months)
- DI (mg/month): cumulative dose (mg) / duration of exposure (months)

Duration of exposure to study drug, average daily dose and DI will be summarized descriptively overall and by indication and formulation.
Summary of duration of exposure of study treatment in appropriate time units will include categorical summaries and continuous summaries (i.e. mean, standard deviation etc.) using appropriate units of time. The duration of exposure to study drug will be categorized into time intervals; frequency counts and percentages of patients with exposure in each time interval will be presented. The derived parameters above will also be listed overall and by indication and formulation using Safety Set.

Dose Changes

The number and percentage of patients with dose interruption, reduction and increase will be summarized overall and by indication and formulation in the safety set. Dose interruption, reduction and increase are defined as follows:

- **Interruption** is defined as any period of zero total daily dose followed by a non-zero dose.
- **Reduction** is defined as any decrease from the immediate prior non-zero total daily dose. Zero daily doses are not regarded as reductions.
- **Increase** is defined as any increase from the immediate prior non-zero total daily dose.

The number and percentage of patients with dose interruption, reduction and increase, along with reasons for dose change will be summarized overall and by indication and formulation using Safety Set.For the purpose of summarizing interruptions and reasons, in case multiple entries for interruption that are entered on consecutive days (for pasireotide s.c.) or on consecutive months (for pasireotide LAR) with different reasons will be counted as separate interruptions. However, if the reason is the same in this mentioned multiple entries on consecutive days or months, then it will be counted as one interruption. Listings of all doses of the study drug along with dose reduction, increase and interruption and reasons for dose change will be presented. The derived parameters above will also be listed overall and by indication and formulation using Safety Set.

7.4 SAFETY ANALYSIS

Safety analyses will be performed on Safety Set. The assessment of safety will be based mainly on the frequency of AEs, AESI and SAEs.

7.4.1 Adverse events (AEs)

Treatment emergent AEs are defined as those that started on or after the study medication, or those that started before study medication but worsened afterwards. AEs starting after 84 days following the last dose of pasireotide LAR treatment and after 30 days following the last dose of pasireotide s.c. treatment are not considered treatment emergent AEs.
Summary tables for adverse events (AEs) have to include only AEs that started or worsened during the on-treatment period, the **treatment-emergent** AEs. However, all safety data

(including those from the post-treatment periods) will be listed and those collected during the post-treatment period are to be flagged.
The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and/or preferred term, severity based on CTCAE grades (version 4.03), type of adverse event, relation to study treatment. The summary will include AEs regardless of study-drug relationship. The same analysis will be repeated for SAEs.
All treatment emergent AEs and SAEs will be listed. In this listing, the information on the relationship to study treatment will be included.
Adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology using the latest available MedDRA version at the time of the analyses and the information of MedDRA version will be specified in the footnote of relevant outputs.
The following selection of AEs will be listed and summarized separately using Safety Set. AEs will be summarized for all grades and for grade 3 or 4 side-by-side.

- AEs
- SAEs
- AEs leading to study drug discontinuation
- AEs requiring dose adjustment or interruption
- AEs requiring additional therapy
- Adverse events of special interest (AESI)

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.

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.

Adverse events of special interest / grouping of AEs

The specific categories of AEs of special interest list for SOM230 are listed in attachment 8.2.

7.4.2 Deaths

Separate summaries for on-treatment death and all deaths (including on-treatment and post- treatment) will be produced by primary system organ class and preferred term overall and by indication and formulation using the Safety Set. On-treatment and all

deaths will be listed overall and by indication and formulation and post treatment deaths will be flagged.

8 ATTACHMENTS

8.1 MAIN PROTOCOL DEVIATION LIST

Protocol Deviation Category	**Description**
Eligibility and Entry Criteria*	I01 Patient is not currently enrolled in a Novartis sponsored study receiving pasireotide and has not fulfilled all their requirements in the parent study
Eligibility and Entry Criteria*	I02 Patient is not currently benefiting from the treatment with pasireotide
Eligibility and Entry Criteria*	I03 Patient has demonstrated non- compliance, as assessed by the investigator, with the parent study protocol requirements
Eligibility and Entry Criteria*	I04 Patient is unwilling and/or not able to comply with scheduled visits, treatment plans and any other study procedures
Informed Consent Criteria*	I05 Informed consent not signed at all.
Informed Consent Criteria*	I06 ICF not signed before patient received study drug
Eligibility and Entry Criteria*	E01 Patients terminated from the parent protocol and is not eligible to participate in the study.
Eligibility and Entry Criteria*	E02 Patient receiving pasireotide in combination with unapproved or experimental treatments
Eligibility and Entry Criteria*	E03 Sexually active male patient not using highly effective contraception
Eligibility and Entry Criteria*	E04 Pregnant or nursing (lactating) women enrolled into the study but did not receive study drug
Eligibility and Entry Criteria*	E05 Women of childbearing potential, not using highly Effective methods of contraception.
Eligibility and Entry Criteria*	E06 Patient is pregnant at study entry (first dose study drug was administered)
Study Procedures Criteria*	D01 Patient met hepatic discontinuation criteria and not withdrawn
Study Procedures Criteria*	D02 Patient met QT discontinuation criteria and not withdrawn
Study Procedures Criteria*	D03 Patient met hyperglycemic Discontinuation criteria and not withdrawn

Study Procedures Criteria*	D04 Patient became pregnant during the study and was not withdrawn
Study Procedures Criteria*	D05 Investigator determines that patient is no longer benefiting from treatment but did not discontinue patient from study
Study Procedures Criteria*	Other Criteria for premature patient withdrawal was met and not withdrawn
Investigation Product (IP) Compliance*	S01 Missed injection of study medication
Investigation Product (IP) Compliance*	S02 Starting dose of pasireotide differs from last dose received in the parent study
Investigation Product (IP) Compliance*	S03 Parent protocol medication taken instead of CSOM230B2412 medication at visit 1
Investigation Product (IP) Compliance*	S04 Dose up/down titration not done as defined in parent protocol
Investigation Product (IP) Compliance	Time window between administration of pasireotide LAR/s.c. not according to the protocol (LAR 28 days ± 7 days / s.c. 84 days ± 14 days from the IP administration date).
Investigation Product (IP) Compliance	Pharmaceutical formulation not administered as defined in the parent protocol
Investigation Product (IP) Compliance*	S06 Time window between administration of pasireotide LAR too short or too long (less than 14 days and more than 56 days from the last monthly injection).
Investigation Product (IP) Compliance	Patient was mistakenly provided Novartis labelled IP
Investigation Product (IP) Compliance	Patient was mistakenly provided expired IP
Investigation Product (IP) Compliance	Due to delays in obtaining regulatory approvals for sponsor change and due to unavailability of the Novartis labelled IP, Recordati labelled IP was used
Investigation Product (IP) Compliance	IP kit discarded by the site staff by mistake
Concomitant Medication Criteria*	M01 Patient took an excluded concomitant Medication
Study Procedures Criteria	IP storage temperature out of range.
Study Procedures Criteria	IP Temperature log is not available at site for a certain period
Informed Consent Criteria*	G01 Informed consent not Appropriately obtained (e.g. Incorrect version signed, new ICF version approved not signed on a consecutive visit, site personnel not delegated signed the ICF, etc.,)
Informed Consent Criteria	Other general ICF documentation errors (e.g. incomplete name/signature, boxes not checked where needed, missing initials on any ICF page where needed, etc.).

Source Document Criteria*	G02 Source Documentation lost
Administrative Criteria*	G03 Study drug administration not properly documented in CRF and drug accountability logs
Serious Adverse Event Criteria*	G04 SAE not reported within 24 hours of learning of its occurrence
Study Procedures Criteria*	G06 Male patient is sexually active and does not use condoms during the study and for 1 months after pasireotide s.c. last dose and 3 months after pasireotide LAR last dose and should not father a child in this period.
Study Procedures Criteria*	G07 Investigator failed to question patient on any possible adverse events and serious adverse events
Study Procedures Criteria*	G08 Investigator failed to assess if the patient was continuing to receive clinical benefit at the visit.
Study Procedures Criteria	Investigator failed to document in eCRF if the patient was continuing to receive clinical benefit at the visit
Visit Schedule Criteria*	G10 Missed visit due to COVID-19
Visit Schedule Criteria*	G11 Visit done outside of study site due to COVID-19
Study Procedures Criteria*	G12 Assessment/ procedure changed due to COVID-19
Study Procedures Criteria*	G13 Drug supply method changed due to COVID-19
Investigation Product (IP) Compliance*	G14 Treatment not given due to COVID-19
Other Criteria*	G15 Discontinuation due to COVID-19
Study Procedures Criteria*	G16 Patient failed to adhere to protocol requirements or visit schedule
Study Procedures Criteria*	G17 Female patient of childbearing potential did not complete diary with dates and outcome of at-home urine pregnancy tests while on study treatment
Study Procedures Criteria	Site staff are allowed to work for limited hours due to Covid 19 restrictions

8.2 LIST 0F AES OF SPECIAL INTEREST

Category	**Adverse Event Term**
AESI Bradycardia related AEs	Atrial conduction time prolongation (PT)
	Atrioventricular block (PT)
	Atrioventricular block complete (PT)
	Atrioventricular block second degree (PT)
	Atrioventricular dissociation (PT)
	Bradycardia (PT)
	Central bradycardia (PT)
	Conduction disorder (PT)
	Defect conduction intraventricular (PT)
	Electrocardiogram PQ interval prolonged (PT)
	Electrocardiogram PR prolongation (PT)
	Electrocardiogram QRS complex prolonged (PT)
	Electrocardiogram QT prolonged (PT)
	Long QT syndrome (PT)
	Paroxysmal atrioventricular block (PT)
	Sinoatrial block (PT)
	Sinus bradycardia (PT)
AESI Coagulation related AEs	Blood fibrinogen decreased (PT)
	Blood thrombin decreased (PT)
	Blood thromboplastin abnormal (PT)
	Blood thromboplastin decreased (PT)
	Coagulation factor IX level decreased (PT)
	Coagulation factor V level decreased (PT)
	Coagulation factor VII level decreased (PT)
	Coagulation factor X level decreased (PT)
	Coagulation factor decreased (PT)
	Hypofibrinogenaemia (PT)
	International normalised ratio abnormal (PT)
	Prothrombin level decreased (PT)
	Prothrombin time prolonged (PT)
	Prothrombin time ratio decreased (PT)
	Thrombin time prolonged (PT)
AESI Gallbladder and biliary related AEs	Bile duct necrosis (PT)
	Bile duct obstruction (PT)
	Bile duct stenosis (PT)
	Bile duct stone (PT)

Category	Adverse Event Term
	Bile output abnormal (PT)
	Bile output decreased (PT)
	Bile output increased (PT)
	Biliary cirrhosis (PT)
	Biliary colic (PT)
	Biliary dilatation (PT)
	Biliary dyskinesia (PT)
	Biliary dyspepsia (PT)
	Biliary fibrosis (PT)
	Biliary fistula (PT)
	Biliary ischaemia (PT)
	Biliary tract disorder (PT)
	Bilirubin conjugated abnormal (PT)
	Bilirubin conjugated increased (PT)
	Bilirubin excretion disorder (PT)
	Bilirubin urine present (PT)
	Bilirubinuria (PT)
	Blood alkaline phosphatase abnormal (PT)
	Blood alkaline phosphatase increased (PT)
	Blood bilirubin abnormal (PT)
	Blood bilirubin increased (PT)
	Blood bilirubin unconjugated increased (PT)
	Cholangiogram abnormal (PT)
	Cholecystectomy (PT)
	Cholecystitis (PT)
	Cholecystitis acute (PT)
	Cholecystitis chronic (PT)
	Cholecystogram intravenous abnormal (PT)
	Cholecystogram oral abnormal (PT)
	Cholelithiasis (PT)
	Cholelithiasis migration (PT)
	Cholelithiasis obstructive (PT)
	Cholestasis (PT)
	Deficiency of bile secretion (PT)
	Endoscopy biliary tract abnormal (PT)
	Gallbladder disorder (PT)
	Gallbladder enlargement (PT)
	Gallbladder fibrosis (PT)
	Gallbladder fistula (PT)
	Gallbladder hypofunction (PT)

Category	Adverse Event Term
	Gallbladder necrosis (PT)
	Gallbladder obstruction (PT)
	Gallbladder oedema (PT)
	Gallbladder operation (PT)
	Gallbladder palpable (PT)
	Haemobilia (PT)
	Hepatitis cholestatic (PT)
	Hepatobiliary disease (PT)
	Hyperbilirubinaemia (PT)
	Jaundice (PT)
	Jaundice cholestatic (PT)
	Jaundice extrahepatic obstructive (PT)
	Obstructive pancreatitis (PT)
	Perforation bile duct (PT)
	Pseudocholelithiasis (PT)
	Ultrasound biliary tract abnormal (PT)
	Urine bilirubin increased (PT)
	X-ray hepatobiliary abnormal (PT)
AESI Growth hormone deficiency related AEs	Blood growth hormone decreased (PT)
	Insulin-like growth factor decreased (PT)
AESI Hyperglycemia-related AEs	Blood glucose increased (PT)
	Blood insulin decreased (PT)
	Diabetes mellitus (PT)
	Diabetes mellitus inadequate control (PT)
	Diabetes with hyperosmolarity (PT)
	Diabetic coma (PT)
	Diabetic hyperglycaemic coma (PT)
	Diabetic hyperosmolar coma (PT)
	Diabetic ketoacidosis (PT)
	Diabetic ketoacidotic hyperglycaemic coma (PT)
	Diabetic ketosis (PT)
	Fructosamine increased (PT)
	Glucose tolerance decreased (PT)
	Glucose tolerance impaired (PT)
	Glucose tolerance test abnormal (PT)
	Glucose urine (PT)
	Glycosuria (PT)
	Glycosylated haemoglobin increased (PT)
	Hyperglycaemia (PT)
	Hyperglycaemic hyperosmolar nonketotic syndrome (PT)

Category	Adverse Event Term
	Impaired fasting glucose (PT)
	Impaired insulin secretion (PT)
	Increased insulin requirement (PT)
	Insulin-requiring type 2 diabetes mellitus (PT)
	Ketoacidosis (PT)
	Ketonuria (PT)
	Ketosis (PT)
	Ketosis-prone diabetes mellitus (PT)
	Monogenic diabetes (PT)
	Type 1 diabetes mellitus (PT)
	Type 2 diabetes mellitus (PT)
AESI Hypocortisolism related AEs	Adrenal insufficiency (PT)
	Adrenal suppression (PT)
	Adrenocortical insufficiency acute (PT)
	Cortisol decreased (PT)
	Cortisol deficiency (PT)
	Cortisol free urine decreased (PT)
	Glucocorticoid deficiency (PT)
	Glucocorticoids decreased (PT)
	Secondary adrenocortical insufficiency (PT)
	Steroid withdrawal syndrome (PT)
AESI Hypotension related AEs	Blood pressure ambulatory decreased (PT)
	Blood pressure decreased (PT)
	Blood pressure diastolic decreased (PT)
	Blood pressure immeasurable (PT)
	Blood pressure orthostatic abnormal (PT)
	Blood pressure orthostatic decreased (PT)
	Blood pressure systolic decreased (PT)
	Hypotension (PT)
	Mean arterial pressure decreased (PT)
AESI Hypothyroidism related AEs	Blood thyroid stimulating hormone decreased (PT)
	Hypothyroidism (PT)
	Myxoedema (PT)
	Myxoedema coma (PT)
	Secondary hypothyroidism (PT)
	Thyroid dermatopathy (PT)
	Thyroid stimulating hormone deficiency (PT)
	Thyroxine free decreased (PT)
	Tri-iodothyronine decreased (PT)
	Tri-iodothyronine free decreased (PT)

Category	Adverse Event Term
AESI Injection site reaction related AEs	Administration site abscess (PT)
	Immediate post-injection reaction (PT)
	Injection site atrophy (PT)
	Injection site bruising (PT)
	Injection site discolouration (PT)
	Injection site discomfort (PT)
	Injection site erosion (PT)
	Injection site erythema (PT)
	Injection site exfoliation (PT)
	Injection site granuloma (PT)
	Injection site haematoma (PT)
	Injection site haemorrhage (PT)
	Injection site hypersensitivity (PT)
	Injection site inflammation (PT)
	Injection site irritation (PT)
	Injection site necrosis (PT)
	Injection site nodule (PT)
	Injection site oedema (PT)
	Injection site pain (PT)
	Injection site pruritus (PT)
	Injection site rash (PT)
	Injection site reaction (PT)
	Injection site swelling (PT)
	Injection site urticaria (PT)
AESI Liver safety related AEs	Alanine aminotransferase abnormal (PT)
	Alanine aminotransferase increased (PT)
	Ammonia increased (PT)
	Aspartate aminotransferase abnormal (PT)
	Aspartate aminotransferase increased (PT)
	Blood cholinesterase abnormal (PT)
	Blood cholinesterase decreased (PT)
	Computerised tomogram liver abnormal (PT)
	Gamma-glutamyltransferase abnormal (PT)
	Gamma-glutamyltransferase increased (PT)
	Guanase increased (PT)
	Hepatic enzyme abnormal (PT)
	Hepatic enzyme decreased (PT)
	Hepatic enzyme increased (PT)
	Hepatic function abnormal (PT)
	Hepatobiliary scan abnormal (PT)

Category	Adverse Event Term
	Hyperammonaemia (PT)
	Hypertransaminasaemia (PT)
	Liver function test increased (PT)
	Transaminases abnormal (PT)
	Transaminases increased (PT)
	Ultrasound liver abnormal (PT)
	Urine bilirubin increased (PT)
AESI Low blood cell related AEs	Anaemia (PT)
	Febrile neutropenia (PT)
	Haematocrit decreased (PT)
	Haemoglobin decreased (PT)
	Leukopenia (PT)
	Lymphocyte count decreased (PT)
	Lymphopenia (PT)
	Neutropenia (PT)
	Platelet count decreased (PT)
	Red blood cell count decreased (PT)
	Thrombocytopenia (PT)
AESI Pancreatitis related AEs	Abdominal compartment syndrome (PT)
	Blood trypsin increased (PT)
	Fat necrosis (PT)
	Hyperlipasaemia (PT)
	Lipase abnormal (PT)
	Lipase increased (PT)
	Pancreatic enzyme abnormality (PT)
	Pancreatic enzymes abnormal (PT)
	Pancreatic enzymes increased (PT)
	Pancreatitis (PT)
	Pancreatitis acute (PT)
	Pancreatitis haemorrhagic (PT)
	Pancreatitis necrotising (PT)
	Pancreatitis relapsing (PT)
	Peripancreatic fluid collection (PT)
AESI QT-prolongation-related AEs	Cardiac arrest (PT)
	Cardiac death (PT)
	Cardiac fibrillation (PT)
	Cardio-respiratory arrest (PT)
	Electrocardiogram QT interval abnormal (PT)
	Electrocardiogram QT prolonged (PT)
	Electrocardiogram repolarisation abnormality (PT)

Category	Adverse Event Term
	Long QT syndrome (PT)
	Loss of consciousness (PT)
	Sudden cardiac death (PT)
	Sudden death (PT)
	Syncope (PT)
	Torsade de pointes (PT)
	Ventricular arrhythmia (PT)
	Ventricular fibrillation (PT)
	Ventricular flutter (PT)
	Ventricular tachyarrhythmia (PT)
	Ventricular tachycardia (PT)