

Clinical Development

SOM230 (Pasireotide)

CSOM230B2406 / NCT01582061

**An open-label, multi-center, expanded access study of
pasireotide s.c. in patients with Cushing's disease
(Seascape)**

RAP Module 3 – Detailed Statistical Methodology



	
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Table 1-1 List of abbreviations


ADA	American Diabetes Association
b.i.d.	<i>bis in diem</i> / twice a day
BMI	Body Mass Index
CI	Confidence Interval
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CSR	Clinical Study Report
ECG	Electrocardiogram
GH	Growth Hormones
HRQOL	Health-related quality of life
IGF-1	Insulin like Growth Factor 1
	
QOL	Quality of Life
RAP	Report and Analysis Plan
SAE	Serious Adverse Event
s.c.	Sub-cutaneous
UFC	Urinary free cortisol
ULN	Upper limit normal
WPAI-GH	Work Productivity and Activity Impairment-General Health

Table 1-2 Document History – Changes compared to previous version of RAP module 3.

Version	Date	Changes
2.0	11-Nov-2011	Initial version
2.1	13-June-2012	<p>Biomarker section modified: Hscores for Immunohistochemistry added</p> <p>Incorporation of changes made after Protocol amendment 3 Objectives and Endpoints</p> <p>As a consequence of extending the study duration, objectives and endpoints have been updated to include an additional time point for analysis at week 48.</p> <p>Description of Study Design</p> <p>This section has been updated to reflect the changes of the starting dose in the European Union and the change of study duration.</p> <p>Subgroup analysis</p> <p>In this section an additional analysis by starting dose has been added.</p> <p>(Adding week 48, starting dose)</p>
2.2	22-July-2012	Revision after 2 nd RAP II meeting (visit windows, dose calculation, biomarker section)
3.0	26-Sep-2012	<p>Final version, Amendment 1</p> <p>Revision after LF review</p> <p>Mean daily dose grouping has been added.</p> <p>Section 4.4 Visit window has been added.</p> <p>Section 4.9 Calculation of changes has been added.</p> <p>Section 4.10 Dose calculations has been added</p> <p>Section 4.12.1.2 CI for continuous variable has been added.</p>
3.1	26- Oct -2012	Removed “Normally Distributed” from section 4.12.1.2
3.2	29-Sep-2016	<p>Draft version , Amendment 2</p> <p>Added Mean 24h-UFC calculation section: the mean UFC calculation at week 12,24and 48 will be based on the last two or three samples collected before the visit , instead of considering only three samples</p> <p>Update sample size calculation</p> <p>Added the publication purposes in the interim analysis</p> <p>Removed biomarker data analysis due to the fact that the vendor never analyzed the data collected for only 7 patients due to Novartis decision</p>
3.3	10-Mar-2017	Final version , Amendment 2

1 Introduction

The RAP document describes the planned statistical analyses for the clinical study report for study SOM230B2406 in the treatment of Cushing's disease. SAS[®] version 9.4 (SAS Institute Inc., Cary, NC, USA) or later will be used for all analyses. Any changes made to this statistical plan after the clinical database lock will be documented separately.

Even written before database lock, this document is using past tense in order to simplify the CSR writing.

2 Study design and treatment

This study is an open-label, uncontrolled, single-arm, multi-center, multi-national expanded access study of pasireotide sub-cutaneous administered twice a day in patients with persistent or recurrent Cushing's disease or with de novo Cushing's disease that are not considered candidates for pituitary surgery (confirmed Cushing's disease).

The starting dose depends on the location of the site:

For sites located in the European Union: the starting dose is 600 µg b.i.d. . However, patients already enrolled in the study at the time of the approval of the amendment 3 are to continue on their current assigned dose.

For site located outside the European Union: the starting dose is 900 µg b.i.d. in all patients except for those with impaired glucose metabolism for whom the starting dose is 600 µg b.i.d.

After a 21-day screening period, patients who satisfied all the inclusion/exclusion criteria started receiving pasireotide. During the first 24-week period, patients had a visit on a weekly basis up to week 4 and then on a 4-week basis. In the second study period, i.e. after the 24 week visit, visits are taking place on 12-week intervals until the end of the study.

Patients remained in the study until pasireotide is approved for commercial use and reimbursed in each respective country or until 31 December -2015 (until 31 December 2016 for sites in South Korea and Brazil), whichever occurred first.

3 Objectives

3.1 Primary

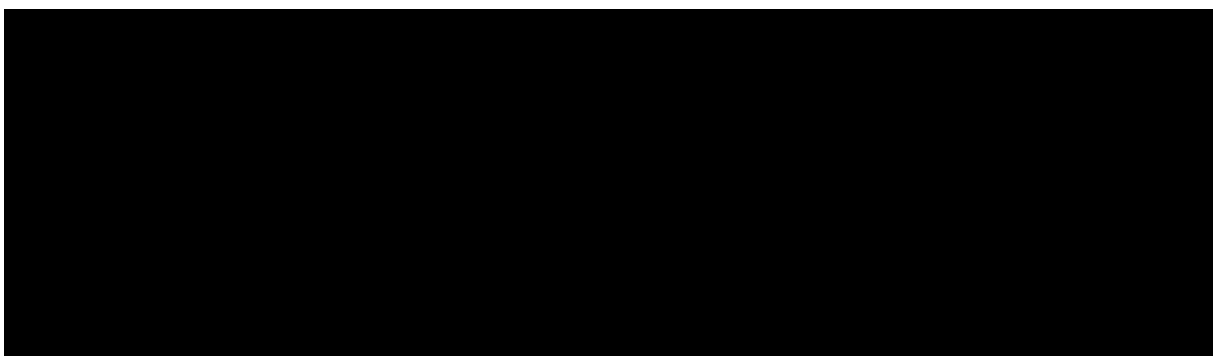
The primary objective is to document the safety of pasireotide s.c. in patients with Cushing's disease.

3.2 Secondary

The secondary objectives are:

- To document the efficacy of pasireotide s.c. in normalizing mean 24h-UFC at Week 12, 24 and 48, separately,
- To document the efficacy of pasireotide s.c. in achieving at least 50% reduction of mean 24h-UFC from baseline at Week 12, 24 and 48, separately,

- To document the changes in clinical signs and symptoms,
- To document the changes in patient-reported outcome questionnaires (CushingQoL and WPAI-GH),
- To document the effects of pasireotide s.c. on the GH/IGF-1 axis.
- To document the overall safety and tolerability of pasireotide s.c. in patients with CD



4 Definitions and general methodology

4.1 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 of the study.

4.2 Study day

Study day is defined to be the number of calendar date from study drug start to any event date.

For events that occurred on or after study drug start date (e.g. lab samples, AEs), study day is computed using following formula:

$$\blacksquare \text{ Study day} = (\text{event date} - \text{study drug start date}) + 1 \text{ day}$$

For events prior to study drug start date (e.g. time of diagnosis), study day is computed using following formula:

$$\blacksquare \text{ Study day} = (\text{event date} - \text{study drug start date})$$

Note that study drug start date is study day 1 and the day before study drug start date is study day -1, therefore there is no study day 0. Unless stated otherwise, one month is defined as a 28 days period.

4.3 Baseline definition

For efficacy and safety evaluations, *baseline assessment* is defined as the last available value (or assessment) prior to study drug start date. If for a given parameter, a patient had no value

(or assessment) prior to study drug start date, baseline will be considered missing for that efficacy and/or safety evaluation.

4.4 Visit windows

It is anticipated that some assessments could be done outside the protocol planned visit windows, for that purpose a computed Visit windows schedule is defined.

Visits after the date of first dose are scheduled weekly for the first 4 weeks and then monthly from study day 28 (visit number 6) to study day 168 (visit number 11). Thereafter every 12 weeks/84 days.

Table 4-1 Visit windows

Study visit	Week	Visit window	Visit window Start*	Visit window Mid-point*	Visit window End*	Visit window Duration
1 (Screening)	-1	-1	-21	0	-1	21
2 (Baseline)	0	0	0	0	0	1
3	1	1	1	7	11	7
4	2	2	12	14	18	7
5	3	3	19	21	25	7
6	4	4	26	28	32	7
7	8	5	33	56	70	28
8	12	6	71	84	98	28
9	16	7	99	112	126	28
10	20	8	127	140	154	28
11	24	9	155	168	182	28
12	36	10	183	252	294	84
13	48	11	295	336	378	84
14	60	12	379	420	462	84
15	72	13	463	504	546	84
16	84	14	547	588	630	84
17	96	15	631	672	714	84
18	108	16	715	756	798	84
19	120	17	799	840	882	84
20	132	18	883	924	966	84
21	144	19	967	1008	1050	84
22	156	20	1051	1092	1134	84

Note: * study day

For summary statistics (tables) for all laboratory data assessment visits are processed as follows:

1. Unscheduled visits are used.

2. Unless stated otherwise, the closest assessment to the mid-point of each visit-window is considered.
3. In case 2 or more assessments are reported on the same day, or have the same distance from the mid-point, i.e. 2 days before, 2 days after, then the mean will be taken.

With regard to mean 24h-UFC, the above rules do not apply as per protocol there are particular definitions, see section 5.2.1 for further details.

All lab assessments are listed.

4.5 Study completion status (end of study)

A patient has **completed the study** after he/she has been followed for 28 days:

1. After having either prematurely discontinued pasireotide s.c.
2. Or, after completing treatment as per protocol (*i.e.* when the study drug is approved for commercial use and reimbursed in each respective country or until 31 December 2015 and until 31 December 2016 for sites in South Korea and Brazil, whichever occurs first).

4.6 Analysis sets

4.6.1 Full analysis set

The Full Analysis Set (FAS) comprises all patients who received at least one dose of pasireotide s.c.

4.6.2 Safety set

The safety set includes all patients who received at least one dose of pasireotide s.c. and had at least one post-baseline safety assessment amongst the following parameters: adverse events, laboratory assessments, vital signs, and ECG.

Please note: the statement that a patient had no adverse events (on the Adverse Event CRF) constitutes a safety assessment.

4.7 Subgroups

Subgroups are based on characteristics measured before study inclusion. Subgroup analyses are described in [Section 6](#).

4.8 Study drug exposure

Duration of exposure (in weeks) will be calculated as

- $Duration\ of\ exposure = (study\ drug\ end\ date - study\ drug\ start\ date + 1) / 7\ days$

The exposure duration includes periods of temporary interruption for any reason.

4.9 Calculation of change

Baseline value is the value collected during the baseline assessment as per the specific definition applying to the parameter, e.g. lab value

Absolute change from baseline is the absolute difference between value at time point t (post-baseline) and value at baseline assessment, it is calculated as:

- *Absolute change from baseline = post-baseline value – baseline value*

Relative change from baseline, or Percentage change from baseline, is calculated as:

- *Relative change from baseline (%) = (absolute change / baseline value) × 100*

4.10 Dose calculations

Total daily dose

The **total daily dose** is the sum of the evening and morning dose:

$$\text{Total daily dose } (\mu\text{g} / \text{day}) = \text{morning dose } (\mu\text{g}) + \text{evening dose } (\mu\text{g})$$

Cumulative dose

The **cumulative dose** (μg) is defined as the total dose administered to a patient over the whole study period.

$$\text{Cumulative dose } (\mu\text{g}) = \sum (\text{morning dose}_i + \text{evening dose}_i)$$

Where i is the day and morning and evening doses are being expressed in μg .

Mean daily dose

Mean daily dose or dose intensity (DI) is defined as:

$$\text{DI } (\mu\text{g}/\text{day}) = \text{Cumulative dose } (\mu\text{g}) / \text{Duration of exposure } (\text{days}).$$

For patients who did not take any drug the mean daily dose is by definition equal to zero.

Similarly, a **4-week mean daily dose** will be computed over a 4-week period in order to allow exploratory analyses on the impact of the dose on clinical safety (adverse events).

Mean daily dose grouping

Mean daily dose category is defined on the mean daily dose considering the following grouping rule:

- **600 μg bid group** includes all patients whose mean daily dose $< 1500 \mu\text{g} / \text{day}$.
- **900 μg bid group** includes all patients whose mean daily dose $\geq 1500 \mu\text{g} / \text{day}$

Note: As mean daily dose groups are based on the actual exposure to the treatment, i.e. not considering days without any study drug administration, reflecting an actual dosing rather than the intended one. That is, 0 dose days are not considered for mean daily dose grouping.

4.10.1 Sample size calculation

No sample size calculation was performed. The planned sample size of approximately 200 patients was chosen based on the expected accrual rates and the planned duration of the trial. The actual sample size may differ from this planned number.

4.11 Analyses

4.11.1 Interim report

It was anticipated that the timing of drug approvals would differ between regions leading to different study completion amongst the different regions (e.g. EU and non-EU sites). Therefore, data from a specific region may have to be reported when all patients from that region have completed the trial.

The primary reason for those analyses are to address health authorities' needs and/or requests, for this reason, data from other regions may be considered in the analysis planned for one region even if the study is still ongoing. . Furthermore, independent of a regional interim analysis additional interim analysis may be performed for regulatory purpose or publication purpose and details will be specified in the study's analysis plan.

Note that this is not a formal interim analysis and does not affect any statistical tests as no hypothesis testing is planned.

4.11.2 Final analysis

The final analysis will be performed when all patients have completed the study.

4.12 Methods for calculating confidence intervals (CI)

4.12.1.1 CI for proportions

Two-sided 95% confidence intervals for proportions will be calculated on the exact method. Confidence intervals will be obtained using Clopper-Pearson confidence intervals ([Clopper and Pearson 1934](#)).

4.12.1.2 CI for continuous variables

Two sided 95% Confidence Interval for continuous variable will be based on the t-distribution. The respective N, Mean and Standard error are outputted in to a data-step and then the TINV function is used to calculate the Confidence Interval as follows:

```
PROC MEANS DATA=test NOPRINT ;  
  VAR age ;  
  OUTPUT OUT=xxtmp N=n MEAN=mean STDERR=stderr ;  
RUN ;  
  
DATA xxtmp1 ; SET xxtmp ;  
  lo = mean - ( TINV ( 0.95 , n-1 ) * stderr ) ;  
  hi = mean + ( TINV ( 0.95 , n-1 ) * stderr ) ;  
RUN ;
```

5 Statistical methods and data analysis

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

A missing category for categorical data will be presented where applicable. Unless otherwise noted, percentages will be based on the number of patients in the relevant population or subgroup.

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 noted otherwise, no imputation for missing data will be performed.

5.1 Primary objective

The primary objective is to document safety of pasireotide s.c. in patients with Cushing's disease (see [Section 3](#)).

5.1.1 Primary variable

The primary variable is the proportion of patients having a drug-related adverse event that was recorded as grade 3 or 4, or as a serious adverse event (see [Section on Adverse events](#) as to how the primary variable will be analyzed).

The analysis will be performed on the Safety set.

5.2 Secondary objectives

5.2.1 Efficacy objectives

These analyses will be performed on the FAS.

Mean 24h-UFC calculation

Screening urinary free cortisol will be measured in two or three 24-hour urine specimens collected during the screening period. The 24h-UFC concentration results from these two or three samples will be averaged to obtain the baseline UFC level. During the study, mean 24h-UFC will be determined at 4-week intervals until week 24. At week 4, 8, 16 and 20, mean 24h-UFC will be determined from two 24-hour urine collections collected on two consecutive days occurring before the visit. At week 12, 24 and 48, the mean 24h-UFC will be determined from two or three 24-hour urine collections, collected over the week before the visit. After week 24, the mean 24h-UFC will be determined at 12-week intervals until end of study visit, from two 24-hour collections during two consecutive days prior to each respective visit (except at Week 48).

Normalization of mean 24h-UFC at Week 12, 24 and 48

The endpoint associated with this objective is the proportion of patients achieving normalization of the mean 24h-UFC (UFC normalization), i.e. the mean 24h-UFC is $\leq 1.0 \times \text{ULN}$.

The number and percentage with corresponding two-sided 95% CI of patients achieving normalization of mean UFC mean 24h-UFC will be presented at Week 12, 24 and 48 (separately).

Note, the mean 24h-UFC is determined from two or three 24h-urine collections collected over the week before the visit.

Mean 24h-UFC imputation

If Week 24 mean 24h-UFC is missing then it will be imputed by the last available mean 24h-UFC values of at least two samples between and including Week 12 and Week 24. If Week 48 mean 24h-UFC is missing then it will be imputed by the last available mean 24h-UFC values of at least two samples between and including Week 12 and Week 48.

Summaries with and without imputing missing Week 24 and Week 48 mean 24h-UFC will be presented.

Similar analyses as defined above will also be performed at all other scheduled post-baseline assessments.

Reduction of mean 24h-UFC $\geq 50\%$ from baseline to Week 12, 24 and 48

The number and percentage with corresponding two-sided 95% CI of patients achieving a reduction of mean 24h-UFC $\geq 50\%$ from baseline to Week 12, 24 and 48 (separately) will be presented.

Similar analyses as defined above will also be performed at all other scheduled post-baseline assessments.

In addition, descriptive summaries of actual and percentage change in mean 24h-UFC from baseline to Week 12, 24 and 48 and all other scheduled post-baseline assessments will be provided.

Changes from baseline to Week 12, 24 and 48 in clinical signs and symptoms

The following clinical signs ([Table 5-1](#)) of Cushing's disease will be assessed by descriptive summaries of the change in systolic BP (standing and sitting), diastolic BP (standing and sitting), BMI, waist circumference and weight from baseline to each post-baseline visit. In addition, the proportion of patients satisfying the clinically relevant thresholds specified in the following table will be calculated along with the exact two-sided 95% CIs at each scheduled post-baseline assessment.

Table 5-1 Clinical Signs

Clinical Sign	Unit, Scale	Clinically relevant threshold (at any time point)
Standing Systolic BP	mmHg	≤ 140 mmHg
Sitting Systolic BP	mmHg, mean of 3 assessments	mean of 3 assessments ≤ 140 mmHg
Standing Diastolic BP	mmHg	≤ 90 mmHg
Sitting Diastolic BP	mmHg, mean of 3 assessments	mean of 3 assessments ≤ 90 mmHg
BMI	kg/m ² , Class levels: < 25.0, 25.0 to < 30.0, ≥ 30.0	% of patients reducing by at least one class level
Waist circumference	cm	Reduction of ≥ 5% Reduction of ≥ 10%
Weight	Kg	Reduction of ≥ 5%

Similar analyses as defined above will also be performed at all other scheduled post-baseline assessments.

The following clinical signs and symptoms (Table 5-2) of Cushing's disease will be assessed by descriptive summaries of changes (or shifts) from baseline to each scheduled post-baseline assessment. The corresponding method of analysis for each clinical sign and symptom are provided in the table.

Table 5-2 Clinical Signs and Symptoms

Clinical signs and symptoms	Scale	Analyses Methods
Facial Rubor (redness)	0=none, 1=mild, 2=moderate, 3=severe	Investigator interpretation, Counts & shifts from baseline.
Hirsutism (Ferriman-Gallway scoring)	0=minimum, 36=maximum Scoring in females only	Investigator interpretation, Ferriman-Gallway score, Actual and % change from baseline
Supraclavicular fat pads	0=none, 1=mild, 2=moderate, 3=severe	Investigator interpretation, Counts & shifts from baseline.
Dorsal fat pads	0=none, 1=mild, 2=moderate, 3=severe	Investigator interpretation, Counts & shifts from baseline.
Muscle strength	0=able to stand easily with arms extended, 1=able to stand after several efforts without using arms as assistance, 2=able to stand only by using arms as assistance 3=completely unable to stand	Direct observation of ability to stand unaided. Counts & shifts from baseline.
Striae	0=none, 1=mild, 2=moderate, 3=severe	Investigator interpretation, Counts & shifts from baseline.
Bruising	0=none, 1=mild, 2=moderate, 3=severe	Investigator interpretation, Counts & shifts from baseline.

Similar analyses as defined above will also be performed at all other scheduled post-baseline assessments.

Changes from baseline to Week 12 ,24 and 48 in Cushing Quality of Life scores

A 12-item Cushing’s syndrome HRQoL questionnaire (CushingQoL, cf. [Webb et al 2008](#)) is implemented in this trial. Patients who completed 9 or more items at a visit are considered evaluable for that visit.

The list of questions includes the following and are answered using a categorical variable ranging from 1 to 5 (see Table 5-3):

1. I have trouble sleeping (I wake up during the night; it takes me a long time to get to sleep, etc.)
2. I have pain that keeps me from leading a normal life
3. My wounds take a long time to heal
4. I bruise easily
5. I am more irritable, I have sudden mood swings and angry outbursts
6. I have less self-confidence, I feel more insecure
7. I’m worried about the changes in my physical appearance due to my illness
8. I feel less like going out or seeing relatives or friends
9. I have had to give up my social or leisure activities due to my illness
10. My illness affects my everyday activities such as working or studying
11. It’s difficult for me to remember things
12. I’m worried about my health in the future

Table 5-3 HRQoL ratings

Answers to HRQoL questions	Rating
‘Always’ or ‘Very much’	1
‘Often’ or ‘Quite a bit’	2
‘Sometimes’ or ‘Somewhat’	3
‘Rarely’ or ‘Very little’	4
‘Never’ or ‘Not at all’	5

Standardized scores and their changes from baseline to Week 12, 24 and 48 will be descriptively summarized.

The standardized scores are calculated as follows:

1. Obtain raw scores, denoted by X, as the sum of all the ratings on all the HRQoL questions for a single patient and the score can range from 12 (worst HRQoL) to 60 points(best HRQoL). Therefore, the lower the score, the greater the impact on HRQoL.
2. Obtain standardized score, Y, for a single patient
 - a. $Y = 100 \cdot (X-12) / (60-12) = 100 \cdot (X-12)/48$. For example, if a patient answers all 12 items with ‘Sometimes’ or ‘Somewhat’, $X = 36$ and $Y = 100 \cdot 24/48 = 50$.

Similar analyses as defined above will also be performed at all other scheduled post-baseline assessments.

Changes from baseline to Week 12 , 24 and 48 in WPAI-GH scores

The WPAI-GH questionnaire is to assess work productivity and activity impairment.

WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes, as follows (see [Reilly 2002](#)):

Questions:

- 1 = currently employed
- 2 = hours missed due to health problems
- 3 = hours missed other reasons
- 4 = hours actually worked
- 5 = degree health affected productivity while working
- 6 = degree health affected regular activities

Scores (multiply scores by 100 to express in percentages):

Percent work time missed due to health: $Q2/(Q2+Q4)$

Percent impairment while working due to health: $Q5/10$

Percent overall work impairment due to health:

$Q2/(Q2 + Q4) + [(1 - Q2/(Q2 + Q4)) \cdot (Q5/10)]$

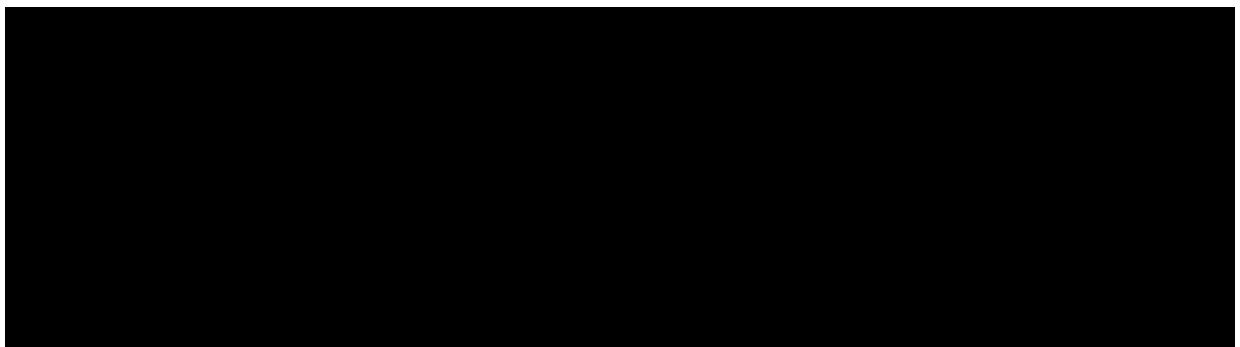
Percent activity impairment due to health: $Q6/10$

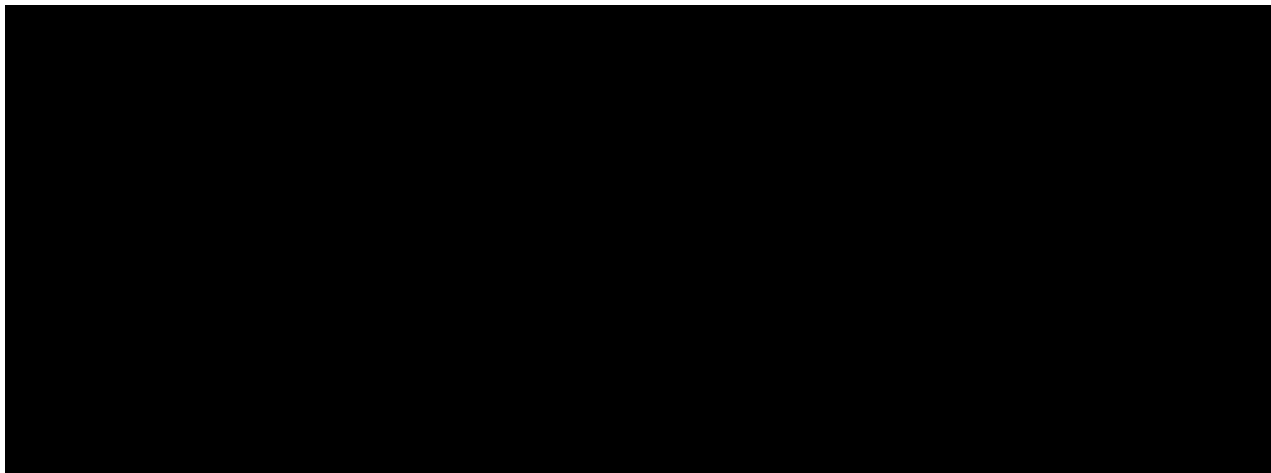
Descriptive summaries of actual and percentage change in mean scores from baseline to Week 12, 24 and 48 will be provided. Similar analyses will also be performed at all other scheduled post-baseline assessments.

Changes from baseline in GH and IGF-I to Week 12, 24 and 48

Descriptive summaries of the absolute and relative change from baseline of GH and IGF-at Week 12, 24 and 48 will be provided.

Similar analyses will also be performed at all other scheduled post-baseline assessments.





5.3 Safety analyses

5.3.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used.

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 28 days after last dose of study medication,
3. Post-treatment period: starting at 29 days after last dose of study medication.

5.3.2 Adverse events

Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period, the *treatment-emergent* AEs. However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre and post-treatment period will be flagged.

For the primary objective of the study, the number and percentage of patients having any drug-related adverse event that was recorded as grade 3 or 4, or as a serious adverse event will be summarized by system organ class and/or preferred term, severity (based on CTCAE grades), and type of adverse event.

In addition, 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), type of adverse event and relation to study treatment. Deaths will be listed and summarized by cause of death.

The following adverse event summaries will be provided:

- Adverse events, suspected to be study drug related that was recorded as grade 3 or 4, or as a serious adverse event, by primary system organ class and/or preferred term and severity (based on CTCAE grades),

- Adverse events, regardless of study drug relationship, by primary system organ class and preferred term,
- Adverse events, suspected to be study drug related, by primary system organ class and preferred term,
- CTC grade 3 or 4 adverse events, regardless of study drug relationship, by primary system organ class and preferred term,
- CTC grade 3 or 4 adverse events, suspected to be study drug related, by primary system organ class and preferred term,
- Adverse events leading to study drug discontinuation, regardless of study drug relationship, by primary system organ class and preferred term,
- Deaths by primary system organ class and preferred term,
- SAEs, regardless of study drug relationship, by primary system organ class and preferred term,
- SAEs, suspected to be study drug related, by primary system organ class and preferred term,
- SAEs leading to study drug discontinuation, regardless of study drug relationship, by primary system organ class and preferred term.

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 2% 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.

5.3.2.1 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 pasireotide treatment (i.e. where pasireotide 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 will be used and documented in CSR. For more detail please refer section 8.

The following adverse event summary will be produced:

- Adverse events of special interest, regardless of study drug relationship, by category, preferred term and maximum CTC grade.

5.3.3 Laboratory abnormalities

The summaries will include all laboratory assessments collected no later than 28 days after study treatment discontinuation. All laboratory data will be listed and those collected later than 28 days after study treatment discontinuation will be flagged in the listings.

For laboratory tests covered by the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, the study's biostatistics and reporting team will grade laboratory data accordingly. 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.

Concentrations below the limit of quantification will not be presented in summary statistics.

The following summaries will be produced for the laboratory data (by laboratory parameter)

- 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,
- Shift tables of fasting glucose and related biochemical parameters using the [ADA \(2010\)](#) or similar low/normal/high classifications to compare baseline to the worst and last on-treatment value.

The following listings will be produced for the laboratory data:

- Listing of patients with laboratory values outside the laboratory reference ranges with values flagged to show the corresponding CTC grades and the classifications relative to the laboratory reference ranges,
- Listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

5.3.4 Vital signs

The parameters collected are: height (cm), weight (kg), body temperature (°C), pulse (beats per minute, bpm), systolic and diastolic blood pressure (mmHg).

The criteria for clinically notable abnormalities 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: $\geq 39.1^\circ\text{C}$
- Weight: Increase from baseline of $\geq 10\%$

- Pulse: ≥ 120 bpm with increase from baseline of ≥ 15 bpm

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: $\leq 35^{\circ}\text{C}$
- Weight: decrease from baseline of $\geq 10\%$
- Pulse: ≤ 50 bpm with decrease from baseline of ≥ 15 bpm

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

- Summary statistic for change from baseline to the worst post-baseline value (in both directions, i.e. from baseline to highest post baseline and from baseline to lowest post-baseline value),
- Number and percentage of patients with at least one post-baseline vital sign abnormality (in both directions, i.e. both elevated and below normal values).

All vital sign assessments will be listed by vital sign parameter. Clinically notable values will be flagged on listings.

5.3.5 Other safety data

5.3.5.1 ECG

The following analyses will be performed for HR, PR, QT intervals and QRS duration, ventricular rate, QTcB (Bazett's formula) and QTcF (Fridericia's formula):

- 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 QT interval, based on both QTcB and QTcF, and newly occurring qualitative ECG abnormalities will be summarized at all scheduled post-baseline time points. A newly occurring ECG abnormality is defined as an abnormal post-baseline finding that was not present at baseline.

Notable criteria for QTcB/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.

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.

5.3.5.2 Gallbladder Ultrasound

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

5.4 Patient demographics/other baseline characteristics

Demographic and other baseline data (including disease characteristics) will be summarized descriptively for the FAS.

5.4.1 Protocol deviations

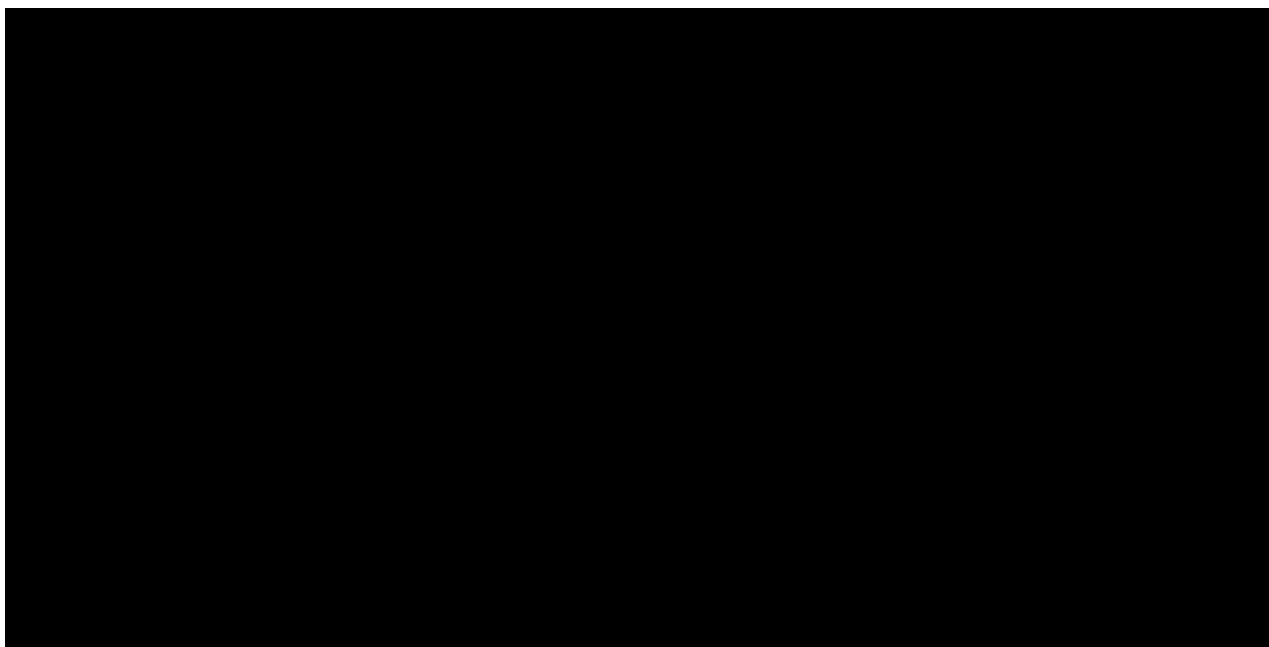
The number and percentage of patients with any relevant protocol deviation will be tabulated. All relevant protocol deviations will be listed. Protocol deviation criteria are specified in the Validation and Planning (VAP) document.

5.5 Concomitant therapies

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized by ATC class and preferred term. These analyses will be performed on the safety set.

5.6 Study medication

Descriptive statistics will be used to summarize the mean daily dose and duration of exposure to pasireotide s.c for all patients and by mean daily dose group (see [section 4.8](#)). The actual and planned doses administered and reason for dose change will be listed. These analyses will be performed on the safety set.



7 Data handling conventions

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

Vital sign Study Completion CMP, ECG and laboratory assessment will be imputed in associating visit date from Visit-based event date imputation (AVIS) (See RAP Module 8).

As describe in the RAP Module 8, any event which has a partial date and requires imputing but has no specific imputation rule, is imputed as follows:

- if the day and month is missing, it will be replaced by 1st of July
- if only the day is missing it will be replaced by the 1st of that month. Partial dates will remain partial in the data listings.

8 Adverse Events of Special Interest (MedDRA v 19.0)

Adverse events of special interest will use MedDRA v 19.0 or the latest version available at a time of data base lock. The current version of grouping of adverse event is present in an attached spreadsheet. The latest version of this spreadsheet will be used at the time of database lock.



SOM230_AESI_Med
DRA 19.0_22Apr2016

The adverse events of special interest list for SOM230 based on MedDRA version 19.1 is available on CREDI:

/CREDI Projects/S/SOM230C/Administrative files/CIS (Clinical Information Sciences)/Biostatistics - SOM230_AESI_MedDRA 19.1_21Nov2016.xls

https://webedi02.eu.novartis.net:8443/webEDI02_non_SSO/drl/objectId/090095a88a122b51

9 References

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