

Clinical Development

Pasireotide/SOM230B

CSOM230B2411 / NCT01915303

**A Phase II trial to assess the efficacy and safety of
pasireotide s.c. alone or in combination with cabergoline in
patients with Cushing's disease**

Statistical Analysis Plan (SAP)

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Document History – Changes compared to previous version.

date	Time point	Reason for update	Outcome for update	Section and title impacted
7/05/2019	Before Dry run	Creation for final version	Initial version	
08/30/2019	Prior to final DBL	Creation of amendment v1.0	<p>For section 8.2.6 new wording was added.</p> <p>For section 6.4.1.1.2 and 6.4.2.1.1 modification was done.</p> <p>Analysis of AESI was changed.</p>	<p>Section 8.2.6, added: However, per protocol amendment 2, group 2 patients time window and study period based on VIS eCRF will be re-mapped into time window of group 1 and end their core phase at week 35, according to the window schema in bookmark18 Table 8-1. All efficacy and safety analysis will be using the time window newly defined.</p> <p>Section 6.4.1.1.2 and 6.4.2.1.1 added >8 to 17 weeks, >17 to 35 weeks</p> <p>Section 6.6.1.</p>
10/27/2019	Post-DBL	Creation of addendum: Karnofsky performance status analysis description was missed although it was included in the protocol.	Karnofsky performance status analysis is added.	Section 6.6.6.

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1 Objectives

This analysis is intended to provide a combined final analysis plan for the core and extension phase of the study. The details of previously performed analysis are described in the document CSOM230B2411_Statistical Analysis Plan_Core phase publication, final version dated 27 March 2017 [4]. This SAP first adapts protocol amendment 2 to combine group 1 (Pasireotide not currently treated) and group 2 (Pasireotide currently treated) into one cohort in most efficacy and safety analysis.

2 Studies considered

Core and extension phase data of the CSOM230B2411 study will be used to perform the analysis.

3 Data source

All analysis will be based on the derived datasets with the following details:

```
// GPSII\CSOM230B\CSOM230B2411\csr_2\analysis_data
```

4 Cut-off date

The cut-off date for this analysis is the final cut-off date for extension phase, 30-Jun-2019 (LPLV).

5 Patient population

5.1 Full analysis set

The Full Analysis Set (FAS): comprises all patients to whom study treatment has been assigned at core phase, including all group 1 and group 2 subjects. FAS will be used in analysis for the core phase.

Extension Full analysis set (Extension FAS): a subset of FAS, included patients to whom study treatment has been assigned in extension phase, including all group 1 and group 2 subjects.

Extension FAS will be used to summarized data from week 43 to final cutoff week data, unless it is specified, EXTENSION FAS and will be used to combine the core and extension phase data for some analyses.

5.2 Safety set

Safety set: includes all patients who received at least one dose of study medication defined in the core and extension study phase.

The safety set will be used to combine the core and extension phase data for all safety analyses and summaries over the visit window with available data. Core phase data will be

summarized from baseline to week 35 at end of the core phase. Extension phase data will be summarized from week 43 to last cutoff week for patients enrolled into extension phase.

5.3 Per-protocol set

The Per-Protocol Set (PPS) consists of a subset of the patients in the FAS who received at least one dose of the study drug and had no major protocol violations. The protocol deviations criteria will be defined prior to database lock in VAP 3 and in section 2.3.2 of [4]. Protocol deviations will be reported for core and extension phase in table and listings.

6 Analyses related to already existing outputs

6.1 Treatment regimen

The following labels for treatment regimens will be used in generating tables and figures where is applicable:

- Pasireotide s.c alone
- Pasireotide s.c. in combination with cabergoline

6.2 Patient disposition

Frequency distributions will be used to summarize the patient disposition at the time of analysis and associated reasons for discontinuation of study medication and study using EXTENSION FAS for the Extension phase. The following will be tabulated for the extension phase:

- Number (%) of patients who are still on-treatment at final cutoff date (based on the absence of the ‘Study Phase Completion - Extension study’ page);
- Number (%) of patients who discontinued treatment (based on completion of the ‘Study Phase Completion – extension Phase’ page with date of discontinuation and reason of discontinuation/ ‘Subject Status’ entered);
- Primary reasons for treatment discontinuation Extension phase (based on discontinuation reasons entered under ‘Subject Status’ in the ‘Study Phase Completion – Extension study’ page).

6.3 Patient demographics and other characteristics - Core and Extension phase

Demographic data (such as age, sex, race, ethnicity, height, and weight), disease characteristics, and other baseline characteristics will be summarized descriptively using the FAS and EXTENSION FAS.

All data collected at baseline such as the history of Cushing's disease (time since diagnosis in months, status of disease, prior pituitary surgery/irradiation, time since prior

pituitary irradiation, duration of prior treatment with pasireotide, baseline symptoms, mean UFC at baseline), will be summarized using descriptive statistics and will be listed as required.

For group 2, the duration of prior treatment with pasireotide (in months) will be summarized with descriptive statistics, as continuous variable and by category (>12 months or missing).

6.3.1 Medical history - Core phase

Medical history and ongoing conditions will be summarized and listed for all patients. Separate summaries will be presented for ongoing and historical medical conditions. The summaries will be presented by primary system organ class and preferred term. Medical history/current medical conditions are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology using the latest version available (Version. 22.0) prior to clinical database lock.

6.4 Treatments (study drug, other concomitant therapies)

6.4.1 Extent of exposure of cabergoline

All study medication data will be summarized using the safety set.

6.4.1.1 Dose intensity and exposure - Core and extension phase

Duration of exposure will be summarized by appropriate descriptive statistics. The following definitions will be used:

Treatment start date: defined as the first date at which a non-zero dose of cabergoline is administered during the study and recorded on the Dosage Administration Record (DAR) eCRF over core and extension phase for safety set.

6.4.1.1.1 Core and extension phase

Treatment end date (extension phase): defined as the last date at which a non-zero dose of cabergoline was administered and recorded on the DAR eCRF for patients who discontinue before the final cutoff date of the extension phase or who complete the extension phase with the final cutoff date recorded on the VIS eCRF.

Duration of exposure (core and extension phase): will be calculated as the number of days from the treatment start date to the treatment end date above, including days with interruptions.

duration of exposure for extension phase = treatment end date (final cutoff date) – treatment start date + 1.

6.4.1.1.2 Dose exposure and intensity

Dose intensity of cabergoline will be calculated for each patient as total cumulative dose at the time of last administration divided by the duration of exposure.

Duration of exposure and dose intensity while in the study will be summarized with descriptive statistics over the core phase. A frequency table will show the number and percentage of patients per duration of exposure category: core phase category (≤ 8 weeks, >8 to 17 weeks, >17 to 35 weeks, >35 to 40 weeks). For core and extension phase: (≤ 8 weeks, >8 to 17 weeks, 17-35 weeks, >35 to 43 weeks, >43 to 98 weeks, >98 to 153 weeks, >153 to 208 weeks, >208 to 263 (up to final week)).

6.4.2 Extent of exposure of pasireotide s.c. alone or in combination with cabergoline

6.4.2.1 Dose intensity and exposure - Core and extension phase

All study medication data will be summarized using the safety set.

Duration of exposure will be summarized by appropriate descriptive statistics. The following definitions will be used:

Treatment start date: defined as the first date at which a non -zero dose of pasireotide s.c. alone or in combination with cabergoline, administered during the study and recorded on the Dosage Administration Record (DAR) eCRF.

Treatment end date (extension phase): defined as the last date at which a non-zero dose of pasireotide was administered and recorded on the DAR eCRF for patients who discontinued before the last cutoff date of the extension phase or who complete the extension phase with the final cutoff date recorded on the VIS eCRF.

Duration of exposure (core and extension phase): will be calculated as the number of days from the treatment start date to the treatment end date above, including days with interruptions.

duration of exposure = treatment end date (extension phase) – treatment start date + 1

6.4.2.1.1 Dose exposure and intensity

Dose intensity of pasireotide s.c. alone or in combination with cabergoline will be calculated for each patient as total cumulative dose at the time of last administration divided by the duration of exposure.

Duration of exposure and dose intensity while in the study will be summarized with descriptive statistics over the core phase. A frequency table will show the number and percentage of patients per duration of exposure category: core phase category (≤ 8 weeks, >8 to 17 weeks, >17 to 35 weeks, >35 to 40 weeks). For core and

extension phase:(≤ 8 weeks, >8 to 17 weeks, 17-35 weeks, >35 to 43 weeks, >43 to 98 weeks, >98 to 153 weeks, >153 to 208 weeks, >208 to 263 (up to final weeks)).

6.5 Efficacy evaluation

6.5.1 Primary efficacy evaluation for core and extension phase

The primary efficacy endpoints are:

- Proportion with corresponding asymptotic 95% CI of patients who attain mean of urinary free cortisol (mUFC) $\leq 1.0 \times \text{ULN}$ at date-cutoff date with pasireotide alone or in combination with cabergoline for FAS and Extension FAS set.

Handling of missing value/censoring/discontinuation is described in [Section 8.3.2](#).

A responder is a patient who has $\text{mUFC} \leq \text{ULN}$.

Last observation carried forward (LOCF) methodology will be used for mUFC assessment for the core phase. The primary efficacy at end of core phase date (week 35) and cut-off of the extension phase will be summarized by baseline mUFC categories. The primary efficacy endpoint will be summarized within each of the three mUFC levels at baseline:

- $1 \times \text{ULN} < \text{baseline mUFC} \leq 2.0 \times \text{ULN}$
- $2 \times \text{ULN} < \text{baseline mUFC} \leq 5.0 \times \text{ULN}$
- $\text{baseline mUFC} > 5.0 \times \text{ULN}$

These analyses will be performed on FAS and EXTENSION FAS.

6.5.2 Secondary efficacy evaluation

The secondary efficacy endpoints will be summarized for the FAS and EXTENSION FAS for parameters from baseline measurements over core phase to week 35 and extension phase from week 43 to final cutoff date at each scheduled assessment:

1. Actual and percentage change in mUFC from baseline to each scheduled visit when UFC is measured until the final cut-off date
2. Proportion of patients with normalized mUFC (i.e $\text{mUFC} \leq 1.0 \times \text{ULN}$) as assessed at each scheduled visit when UFC is measured until the final cut-off date
3. Proportion of patients, at each visit, who attained $\text{mUFC} \leq 1.0 \times \text{ULN}$ (controlled) or have at least 50% reduction (partially controlled) from baseline in mUFC as assessed at

each scheduled visit when UFC is measured until the final cut-off date

4. Duration of controlled or partially controlled response is defined as the period starting from the date of patient's first normalization ($mUFC \leq 1.0 \times ULN$) or at least 50% reduction from baseline up to the date when the patient's $mUFC > 1.0 \times ULN$ and the reduction from baseline falls to less than 50% from the first time until the final cut-off date

5. Actual and percentage changes from baseline, at each scheduled post baseline visit, in plasma ACTH and serum cortisol over visit time window until the final cut-off date

6. Actual and percentage change from baseline over visit time window in clinical symptoms of Cushing's disease: blood pressure, body mass index, waist circumference, fasting serum lipid profile, and weight until the final cut-off date

7. Change from baseline in clinical signs of Cushing's disease: facial until the final cut-off date

8. Rubor, supraventricular and dorsal fat pads, hirsutism, striae (via photographs) and muscle strength until the cut-off date

9. Change from baseline in standardized scores, as measured by the Cushing's QOL and SF-12v2 over time until the final cut-off date

10. Toxicity assessed by using the National Cancer Institute-Common Toxicology Criteria Adverse Events version 4.0 (NCI-CTCAE v.4) and for laboratory assessments (biochemistry, hematology, urinalysis); special safety assessments (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 non-drug therapies will be assessed from study enrollment until the final safety date cutoff visit.

Assess the changes in mUFC from baseline to study end at each scheduled visit where UFC is measured – Core and extension phase

Descriptive summaries of actual and percentage change in mean 24h-UFC from baseline to each scheduled visit where UFC is measured will be provided along with corresponding two-sided 95% CIs.

Assess overall efficacy of pasireotide alone or in combination with cabergoline as measured by controlled and partially controlled mUFC levels at each scheduled visit until the final cut-off date

Proportion patients with normalized mUFC (i.e. $mUFC \leq 1.0 \times ULN$) at each scheduled visit will be reported along with its corresponding 95% CI until the final cut-off date

Proportion of patients who attained $mUFC \leq 1.0 \times ULN$ (controlled) or have at least 50% reduction (partially controlled) at each scheduled visit will be reported along with its corresponding 95% CI. If mUFC is missing, no imputation will be done.

Evaluate the duration of controlled or partially controlled mUFC response – Core and extension phase

Duration of controlled or partially controlled response is defined as the period starting from the date of patient's first normalization ($mUFC \leq 1.0 \times ULN$) or at least 50% reduction from baseline up to the date when the patient's $mUFC > 1.0 \times ULN$ and the reduction from baseline falls to less than 50% for the first time. Patients without a loss of response will be censored at their last available mean UFC assessment date (during the core phase). The median and 95% confidence interval of duration of response will be derived from Kaplan-Meier method.

Assess the effect on plasma ACTH and serum cortisol - Core and extension phase

Plasma ACTH and serum cortisol concentrations will be summarized using descriptive statistics at scheduled visit window for core and extension phase. Actual and percent changes from baseline at each scheduled post baseline visit will also be presented along with 95% CIs. Mean serum cortisol and plasma ACTH results over time will be presented graphically.

Assess the effect of continuous measures of clinical symptoms of hypercortisolism - Core and extension phase

Actual and percentage change from baseline in the following clinical symptoms of Cushing's disease (blood pressure, body mass index, waist circumference, fasting serum lipid profile and weight) will be assessed over time window using descriptive statistics.

Fasting serum lipid profile includes four basic parameters: total cholesterol, HDL cholesterol, LDL cholesterol and total protein.

Assess the effect on the categorical measures of clinical signs of hypercortisolism - Core and extension phase

Change in clinical signs of Cushing's disease: facial rubor, supraclavicular and dorsal fat pads, hirsutism, striae and muscle strength will be assessed by descriptively summarizing changes and shifts from baseline to each timepoint. Two assessors blinded to the visit number will score each qualitative endpoint (facial rubor, hirsutism, supraclavicular and dorsal fat pads and striae) by review of duplicated photographs. The investigator will adjudicate non-agreeing assessments. Table 2-2 [4] describes scales and endpoint definitions for each of these assessments. For each clinical sign, descriptive summary statistics will be presented.

6.6 Safety parameters and analysis

Safety and tolerability assessments include AEs, vital signs (blood pressure, heart rate, body temperature), blood glucose (fasting plasma glucose, Hemoglobin A1c), hormones (IGF -1, TSH/free T4), liver enzymes (AST, ALT, alkaline phosphatase, γ GT, total bilirubin), hematology, electrolytes, gallbladder ultrasound and ECGs.

All the safety analysis will be over core and extension phase combined based on safety set.

6.6.1 Adverse events (AE)

All adverse events and the cause of death, as recorded on the completion CRF pages, will be coded using the latest available version of the MedDRA coding dictionary that provides the system organ class (SOC) and preferred term (PT) information.

AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

The CTC/severity grade will not be imputed if missing. CTC grade 5 (death) will not be used in this study.

The incidence of treatment-emergent AEs, during the core phase and during the overall on- treatment period, will be summarized by system organ class (SOC), preferred term (PT) and severity (based on NCI-CTCAE v.4 grades), type of adverse event, relation to study treatment.

A patient with multiple occurrences of an AE will be counted only once in the respective AE category

The following selection of treatment-emergent AEs will be listed and summarized for safety set from study start to final cut-off date for safety set:

- AEs regardless of study drug relationship
- AEs suspected to be study drug-related
- SAEs regardless of study drug relationship
- AEs leading to study drug discontinuation, regardless of study drug relationship
- AEs leading to study drug discontinuation, suspected to be study drug-related
- AEs requiring dose adjustment or study-drug interruption, regardless of study drug relationship
- AEs requiring additional therapy, regardless of study drug relationship
- AEs excluding SAEs
- Adverse events of special interest by type

Specific groupings of AEs of special interest will be considered and the number of patients with at least one event in each grouping ("category") will be reported. Such groups consist of AEs 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 AEs which are similar in nature (although not identical) within safety set. The specific groupings of AEs as defined in the latest documentation available prior to database lock (in [[Cabinets/CREDI Projects/S/SOM230B/Integrated Medical Safety/Safety Profiling and Signal detection/Signal detection]]).

The following table will be produced:

- AEs of special interest by type (any AE, AE suspected to be drug-related, SAE, AE leading to discontinuation, AE requiring dose adjustment), PT and maximum Common Terminology Criteria (CTC) grade.

6.6.2 Laboratory evaluation

For laboratory data assessments, data from all sources (central and local laboratories) will be combined. All laboratory assessments will be listed and those collected outside of the on- treatment period will be flagged in the listings. All laboratory values will be converted into SI units.

All the lab analysis over core and extension phase will be based on safety set. Study baseline will be used in analysis.

Laboratory data will be classified into CTC grades according to the NCI Common Terminology Criteria for Adverse Events CTCAE) v4.03. A severity grade of 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For some laboratory tests, CTC grades are defined in two directions (low and high, e.g. for potassium: hypokalemia and hyperkalemia). The two directions will be analyzed separately.

The following summaries will be produced for the laboratory data (by laboratory parameter and direction of abnormality, as applicable) over core (baseline to week 35) and extension phase (from week 43 to final cutoff) for safety set:

- Shift tables using CTC grades to compare baseline to the worst post-baseline value.
- For laboratory test where NCI-CTCAE v4.03 grades are not defined, shift tables using the low/normal/high/ (low and high) classification will be produced/used to compare baseline to the worst on-treatment value.
- Listing of all laboratory data with values flagged to show the corresponding NCI - CTCAE v4.03 grades and the classifications relatives to the laboratory

normal ranges.

Patients with laboratory values outside the normal range will be listed and flagged to show the corresponding CTC grades and the classifications relative to the laboratory reference ranges. In addition, laboratory values of patients with laboratory abnormalities of CTC grade 3 or 4 will be presented in separate listings.

Liver function tests (LFTs) of interest are total bilirubin (TBILI), ALT, AST and ALP. LFTs will be summarized over core and extension phase based on safety set:

- Shift tables of baseline vs. worst post-baseline on-treatment values for the categories:
 - $TBILI \leq 2xULN$, $TBILI > 2xULN$ and missing TBILI
 - $ALT \leq 3xULN$, $ALT > 3xULN$ and missing ALT
 - $AST \leq 3xULN$, $AST > 3xULN$ and missing AST
 - ALT or $AST \leq 3xULN$, ALT or $AST > 3xULN$ and missing ALT or AST
 - $ALP < 2xULN$, $ALP \geq 2xULN$ and missing ALP
- Frequency counts and percentages of patients with worst post -baseline on-treatment values in the categories:
 - $ALT > 3xULN$, $ALT > 5xULN$, $ALT > 10xULN$, $ALT > 20xULN$
 - $AST > 3xULN$, $AST > 5xULN$, $AST > 10xULN$, $AST > 20xULN$
 - AST or $ALT > 3xULN$, AST or $ALT > 5xULN$, AST or $ALT > 10xULN$, AST or $ALT > 20xULN$
 - $TBILI > 2xULN$
 - Concurrent $ALT > 3xULN$ and $TBILI > 2xULN$
 - Concurrent $AST > 3xULN$ and $TBILI > 2xULN$
 - Concurrent AST or $ALT > 3xULN$ and $TBILI > 2xULN$
 - Concurrent AST or $ALT > 3xULN$ and $TBILI > 2xULN$ and $ALP < 2xULN$
 - Concurrent AST or $ALT > 3xULN$ and $TBILI > 2xULN$ and $ALP \geq 2xULN$

Concurrent measurements are those occurring on the same date.

In addition, a listing of all TBILI, ALT, AST and ALP values for patients with a post-baseline TBILI > 2xULN, ALT > 3xULN or AST > 3xULN will be provided.

Renal Disease (MDRD) will be summarized over core and extension phase based on safety set:

- Shift tables of baseline vs. worst post-baseline on-treatment values
- Frequency counts and percentages of patients with worst post-baseline on-treatment values

The minimum of all the post baseline assessments is the worst value for MDRD.

For calcium, the corrected calcium will be used for analysis. Corrected calcium will be derived using the reported total calcium value and albumin at the same assessment using the following formula:

$$\text{Corrected Calcium (mg/dL)} = \text{Calcium (mg/dL)} - 0.8 [\text{Albumin (g/dL)} - 4]$$

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1), calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory CTC grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

6.6.3 Vital signs and weight for core and extension phase

Vital signs (body temperature, sitting pulse, sitting blood pressure), weight and waist circumference will be summarized and listed. Patients with clinically notable vital sign values will be flagged in the listing.

Vital sign analysis will be summarized over core (baseline to week 35) and extension phase (week 43 to final cutoff) based on safety set. Study baseline will be used in analysis.

The criteria for clinically notable abnormalities are defined as follows:

- Systolic BP: ≥ 180 mmHg and an increase ≥ 20 mmHg from baseline
 ≤ 90 mmHg and a decrease ≥ 20 mmHg from baseline
- Diastolic BP: ≥ 105 mmHg and an increase ≥ 15 mmHg from baseline
 ≤ 50 mmHg and a decrease ≥ 15 mmHg from baseline
- Pulse rate: ≥ 120 bpm with increase from baseline of ≥ 15 bpm
 ≤ 50 bpm with decrease from baseline of ≥ 15 bpm
- Body temperature: $\geq 39.1^\circ\text{C}$

$\leq 35^{\circ}\text{C}$

- Weight: Increase from baseline of $\geq 10\%$
decrease from baseline of $\geq 10\%$

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

- Number (%) of patients with clinically notable abnormalities in Vital signs at any post- baseline time point
- Summary statistic for change from baseline to each post-baseline time points.

Baseline = last value prior to or on the first dose during the study. After baseline, the value closest to the target day (i.e. visit window mid - point) is analyzed if a patient had more than one value within a time window.

6.6.4 ECG

ECG analysis will be summarized over core (baseline to week 35) and extension (week 43 to final cutoff) phase based on safety set. Study baseline will be used in analysis.

The following analyses will be performed for RR, 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 until final cut-off date in extension phase
- Summary statistics of changes from baseline at each scheduled post-baseline time point until final cut-off date in extension phase
- Listing of ECG data (scheduled and unscheduled visits)

Number (%) of patients with a notable QT interval, based on both QTcB and QTcF will be summarized for extension phase on -treatment period separately. ECG shift table based on notable values will be summarized. Notable criteria for QTcB/QTcF include:

- >450 ms at any post-baseline time point and ≤ 450 ms at baseline,
- >480 ms at any post-baseline time point and ≤ 480 ms at baseline,
- >500 ms at any post-baseline time point and ≤ 500 ms at baseline,
- An increase from baseline > 30 ms at any post-baseline time point ,
- An increase from baseline > 60 ms at any post-baseline time point.

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

6.6.5 Gallbladder ultrasound

The findings of the gallbladder imaging (presence of gallstones, presence of sludge, dilatation of ductal system) will be summarized at each visit using frequency tables for safety set over core and extension phase.

6.6.6 Karnofsky performance status

The Karnofsky performance status will be summarized at available visits mentioned in Table 7-1 of protocol by performance status category using counts and percentages.

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