NOVARTIS

Clinical Development

Pasireotide, SOM230

CSOM230B2219 / NCT02060383

A multi-center, randomized, open-label, Phase IV study to investigate the management of pasireotide-induced hyperglycemia with incretin based therapy or insulin in adult patients with Cushing's disease or acromegaly

Statistical Analysis Plan (SAP)

Author:	▮▮▮▮ Trial Statistician
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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
15-Aug-2014	Prior to DB lock	Creation of final version	N/A - First version	NA
07-Feb-2018	Prior to DB lock	Creation of amendment 1	Change from RAP module 3 to new SAP template.	Throughout the SAP, the sections from the previous RAP M3 have been mapped to the relevant section in the SAP template.
			Update of sample size section following protocol amendment 2 which removed the protocol requirement to randomize the equal number of patients with Cushing's disease and Acromegaly.	In Section 3.1, sample size was updated in line with protocol amendment 2.
			Clarification that reported but unreliable serum creatinine values (due to technical malfunction) are excluded from summary tables.	Section 2.8.3
			Addition of AE language for safety disclosure at CT.gov / EudraCT.	Section 2.8.2.4
			Addition of location of PTs for AEs of special interest.	Section 2.8.2.5
			Updated pasireotide nomenclature from pasireotide LAR to pasireotide long-acting	Various sections
			Addition of diabetic status definition, and analysis of change in this status during the study	Section 2.1.1.6 & Section 2.7.6
			Addition of analysis of change in HbA1c categories	Section 2.7.5
25-Jun-2018	Prior to DB lock	Creation of amendment 2	Update of diabetic status definition to be aligned with protocol	Section 2.1.1.6
			Rewording of supportive analysis for the primary	Section 2.5.4
			Addition of potential subgroup analysis by	Section 2.7

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			disease for secondary efficacy objectives	
			Correction of reference to Sections in Table 1-1	Section 1.3

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List of abbreviations

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

1   Introduction

This document describes the detailed statistical methodology to be used in analyzing the data collected consequent to study CSOM230B2219 in patients with Cushing's disease or acromegaly.

The study will be analyzed when all treated patients have completed the study or discontinued earlier, and the final CSR will be produced.

The data from all centers participating in the trial will be combined, so that an adequate number of patients will be available for analysis. The statistical analysis methods described in this SAP will focus on the analysis of the data in the core study. Similar methods will be applied to the analyses in the extension phase as appropriate.

All decisions regarding final analysis, as defined in the SAP document, have been made prior to database lock of the study data.

1.1   Protocol amendments

At the time of finalization of this document the original study protocol had undergone three amendments, as summarized below.

Amendment 1, 08-Aug-2014

Amendment 1 amended visit schedule by adding Week 1 in pasireotide s.c. for ECG and liver function test, and adding Week 3 in pasireotide long-acting for ECG per health authorities request. The inclusion/exclusion criteria are modified in line with adverse drug report profile or to account for gender difference. In addition, the safety follow-up of pasireotide long-acting was updated to 84 days instead of 56 days to ensure 5 times elimination half-life. Wash out periods of other SSAs and previous exposure to pasireotide was updated.

Amendment 2, 29-Sep-2016

As of 9-Sep-2016, 166 patients have been enrolled (49 patients with Cushing's disease and 117 patients with acromegaly). Of the 166 patients enrolled in the trial, out of the planned 79 patients have been randomized (20 Cushing's disease and 30 acromegaly).

The rationale of this amendment 2 is to remove the protocol requirement to randomize the equal number of patients with Cushing's disease and Acromegaly (a total of 79 patients).

In protocol amendment 1, the target was to randomize 79 patients (42 in Cushing's disease and 37 in acromegaly) to obtain 68 randomized patients (34 with Cushing's disease and 34 with acromegaly, who completed at least 8-week randomized treatment without any rescue medication).

Cushing's disease is a rare disease with a low incidence and prevalence and the recruitment of these patients in clinical studies is challenging. In the present study, the availability of this patient population has been lower than expected and consequently, more patients with acromegaly than patients with Cushing's disease are being screened and ultimately randomized. Despite the fact that patients with Cushing's disease and Acromegaly exhibit insulin resistance and metabolic abnormalities secondary to different mechanisms and that the severity of

hyperglycemia might differ, the effect of pasireotide on glucose metabolism is expected to be the same in both populations (i.e. increase of blood glucose levels by decreasing insulin and incretin secretion). Therefore, the proportion of randomized patients from each disease group is not expected to affect the scientific value of the study.

Amendment 3, 17-Mar-2017

Clarification regarding the protocol visits included in the 28-day Safety follow-up for Cushing's disease patients receiving pasireotide s.c and the 84-day Safety follow-up for acromegaly patients receiving pasireotide long-acting as follows:

- Eligible patients as per protocol who are transitioning to a roll-over study or local access program will not be required to perform the safety follow-up visit (779) as patients will continue to be monitored for safety.

- Eligible patients as per protocol who are transitioning to commercial drug will be required to perform the safety follow-up visit (779).

- Re-insertion of the missing Figure 6-1 QT Prolongation Safety Management.

- Allow a ± 3 day visit window for Cushing's patients. Visit windows for Acromegaly patients will remain unchanged as per Table 7-1.

1.2   Study design

This is a Phase IV, multi-center, randomized, open-label study. Eligible patients will start pasireotide s.c. for Cushing's disease and pasireotide long-acting for acromegaly.

Patients currently treated at screening visit with pasireotide s.c. or LAR are eligible if they have an elevated FPG > ULN or a diagnosis of diabetes (FPG ≥ 126 mg/dL on two occasions or HbA1c ≥ 6.5% or a random plasma glucose ≥ 200 mg/dL with classic symptoms of hyperglycemia (polydipsia, polyphagia and polyuria)) during screening period. For patients naive to pasireotide, if previously normo-glycemic patients experience increases in their fasting blood glucose based on pre-defined glycemic criteria while on pasireotide, they will start anti-diabetic treatment using metformin. If they continue to experience increases in their fasting blood glucose within the first 16 weeks, they will be randomized in a 1:1 ratio to receive treatment with incretin based therapy (sitagliptin followed by liraglutide) or insulin for approximately 16 weeks. The effect on glycemic control will be evaluated up to 32 weeks.

To ensure a similar distribution of patients expected to develop mild/moderate/severe hyperglycemia in both treatment arms, randomization will be stratified according to the levels of the following two factors:

- Disease:
    a. Cushing's disease
    b. Acromegaly
- Glycemic status at baseline:
    a. HbA1c < 7 %
    b. HbA1c ≥ 7%

Patients who are not randomized by Week 16 (of pre-randomized period) will have their Core End of Phase (EOP) visit on Week 16. Patients who are randomized will have their Core EOP visit 16 weeks post-randomization.

The total duration of the core study treatment will be a maximum of 32 weeks. Forpatients who do not continue into the extension phase, the last injection of pasireotide s.c. on study will be 1 day prior to Core EOP visit and the last injection of pasireotide long-acting on study will be 4 weeks prior to Core EOP visit.

All patients who will not continue pasireotide treatment must have safety follow-up evaluations after the Core (or Extension) EOP visit, which will be 84 days after the last dose of pasireotide long-acting treatment and 28 days after pasireotide s.c. treatment.

Data Cutoff for Analyses

Patients who discontinue study drug (pasireotide s.c. or pasireotide long-acting) will be considered withdrawn from the study after the final visit assessments and the final safety follow-up visit are performed or when it is clear that the patient will not return for final visit assessments and/or final safety follow-up visit. The CSR will be generated after all patients have completed the study or discontinued earlier. The results within the CSR will be split to show results for the core phase only, then then also for the overall study (core and extension combined). For the two randomized arms, the core phase results will be split into the pre-randomized and randomized treatment periods as necessary.

Figure 1-1   Study design schema
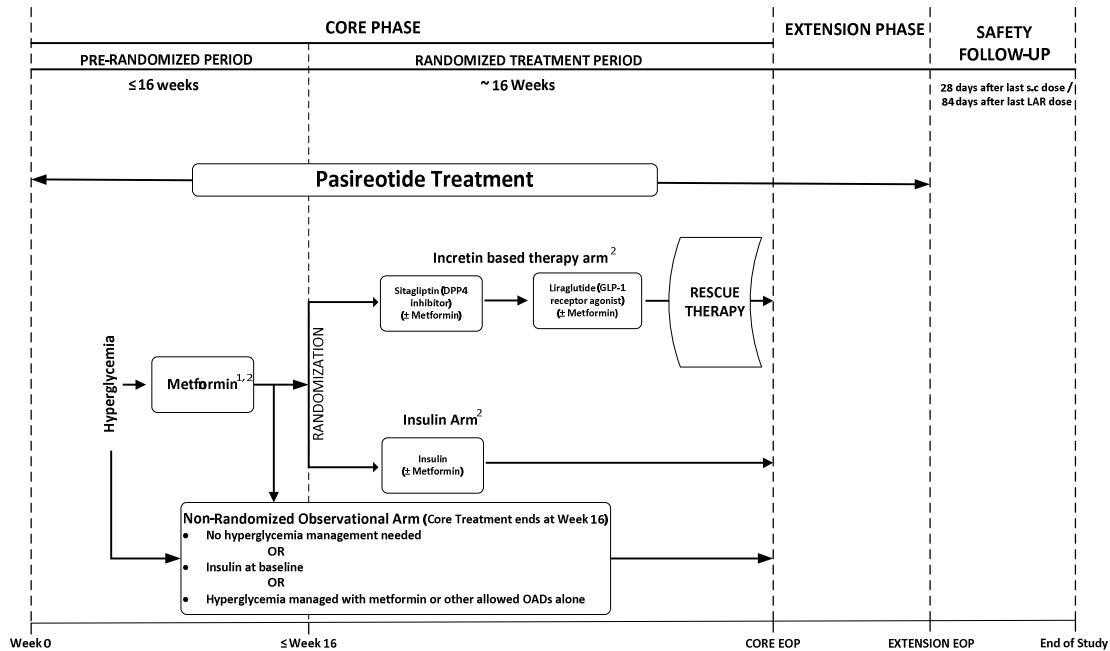
[1] Patients that cannot tolerate metformin or have a contraindication to metformin will be randomized immediately if the average fasting SMBG is ≥ 126 mg/dL on 3 consecutive days.
[2] Patients can continue on allowed OADs at the discretion of the investigator.
Note: The patients can continue on the extension phase until the last patient randomized on the core study completes treatment for 16 weeks post-randomization, or when pasireotide is available commercially or when a local access program is available

1.3   Study objectives and endpoints

The study objectives and related endpoints as specified in the protocol are given in Table 1-1.

Table 1-1   Study objectives

Objective	Endpoint	Analysis
Primary		Refer to Section
To evaluate the effect of treatment with incretin based therapy vs. insulin on the 16-week glycemic control in patients with Cushing's disease or acromegaly who develop or worsen hyperglycemia on pasireotide, and cannot be controlled by metformin alone or other background anti-diabetic treatments	Change in HbA1c from randomization to approximately 16 weeks in the incretin based therapy arm and insulin arm	2.5
Secondary		Refer to Section
To evaluate the overall effect of anti-diabetic intervention on glycemic control in patients with Cushing's disease or acromegaly	- Change in HbA1c and FPG from baseline to Core EOP (End of Phase) in patients who received pasireotide by treatment group	2.71
To evaluate the sustainability of glycemic control in the incretin based therapy arm and the insulin arm in Cushing's disease patients treated with pasireotide s.c. and acromegaly patients treated with pasireotide long-acting	- Proportion of patients with ≤ 0.3% HbA1c increase from baseline to Core EOP per randomized arm	2.7.2
	- Change in HbA1c and FPG from randomization over time and to Core EOP (only for FPG) per randomized arm	2.7.3
	- Proportion of patients who required anti-diabetic rescue therapy with insulin per randomized arm	2.7.4
	- Proportion of patients with HbA1c at the end of the core and extension phases in the following categories: • HbA1c < 6.5% • 6.5% ≥ HbA1c < 7% • HbA1c ≥ 7%	2.7.5
	- Change in diabetic status during the core and extension phases (diabetic status is defined in section 2.1.1.6)	2.7.6
To evaluate the safety and tolerability of pasireotide in combination with anti-diabetic treatments	- Toxicity will be assessed using NCI-CTC criteria version 4.03 for adverse events.	3.1.2
	- Incidence of hypoglycemia events (# of episodes, # of patients)	3.1.4.2
	- Clinical chemistry, hematology, urinalysis assessments	3.1.3
	- ECGs	3.1.4.1

Objective	Endpoint	Analysis
	- Special safety assessments: Thyroid function tests, pancreatic safety tests (for anti-diabetic treatments) and gallbladder examinations	3.1.4.3 3.1.4.4

2   Statistical methods

2.1   Data analysis general information

The primary and final analysis will be performed by Novartis. SAS version 9.4 or later will be used to perform all data analyses and to generate tables, figures and listings.

2.1.1   General definitions

Patients with Cushing's disease will take pasireotide s.c., and patients with acromegaly will take pasireotide long-acting. Herein, *study drug* is used to reference pasireotide across this document.

In addition, for the purpose of analysis, the patients will be grouped into randomized patients, and non-randomized patients group, forming a total of five mutually-exclusive treatment groups based on the anti-diabetic treatment received:

Randomized treatment groups

1. Incretin based therapy group
2. Insulin group

Non-randomized treatment groups

3. Baseline insulin group - includes patients who receive insulin at baseline and thus not randomized.
4. Oral anti-diabetic (OAD) treatment group - patients who developed hyperglycemia that can be controlled by metformin or their background anti-diabetic treatment and thus not randomized
5. No anti-diabetic treatment (NAD) group - includes patients who do not receive any anti-diabetic treatment during the core phase of the study and thus not randomized.

The NAD group, baseline insulin group, and OAD group are the three non-randomized groups that will be treated for 16 weeks during the core phase. The core treatment period of the two randomized arms, i.e., incretin based therapy group and insulin group, is varied and can be up to 32 weeks depending on when patients get randomized.

2.1.1.1   Study day

Study day 1 is the date of first administration of study drug.

The study day for an event that occurs prior to study day 1 will be calculated as (date of event – date of first administration of study drug).

The study day for an event that occurs on or after study day 1 will be calculated as (date of event – date of first administration of study drug) + 1.

2.1.1.2   Baseline

For efficacy and safety evaluations, the last available pre-dose assessment is taken as "baseline" assessment. If several measurements are taken on the same day, the last one prior dose is used as measurement of that day.

2.1.1.3 Visit number

The time point (Day/Week) associated with an assessment, will be determined by the visit number assigned to the corresponding assessment in the database. The mappings of visit numbers to time points in the core study and the extension phases are provided in Table 2-1 and Table2-2.

Table 2-1   Visit number during the core phase

Core phase visit	Day/Week	Clarifying notes
Visit 1	Day -21 to Day -1	Screening
Visit 2	Day 1/PRW0	Baseline
Visit 401	Day 8/PRW1	Pre-randomization period
Visit 3	Day 15/PRW2	Pre-randomization period
Visit 402	Day 22/PRW3	Pre-randomization period
Visit 4	Day 29/PRW4	Pre-randomization period
Visit 5	Day 57/ PRW8	Pre-randomization period
Visit 6	Day 85/ PRW12	Pre-randomization period
Visit 7	R-Day1/RW0	Randomization period
Visit 8	R-Day15/RW2	Randomization period
Visit 9	R-Day29/RW4	Randomization period
Visit 10	R-Day43/RW6	Randomization period
Visit 11	R-Day57/RW8	Randomization period
Visit 12	R-Day71/RW10	Randomization period
Visit 13	R-Day85/RW12	Randomization period
Visit 14	R-Day99/RW14	Randomization period
Visit 777	R-Day113/RW16	End of treatment in core phase
Visit 779	28 days after last s.c. dose or 84 days after last LAR dose	End of study/Follow-up

Table 2-2   Visit number during the extension phase

Extension phase visit	Day/Week	Clarifying notes
Visit 15	E-Day 1/EW0	Long term extension
Visit 16	E-Day 29/EW4	Long term extension
Visit 17	E-Day 57/EW8	Long term extension

Extension phase visit	Day/Week	Clarifying notes
Visit 15	E-Day 1/EW0	Long term extension
Visit 18	E-Day 85/EW12	Long term extension
Visit 19	E-Day 113/EW16	Long term extension
Visit 20	E-Day 141/EW20	Long term extension
Visit 21	E-Day 169/EW24	Long term extension
Visit 22	E-Day 197/EW28	Long term extension
Visit 23	E-Day 225/EW32	Long term extension
Visit 24	E-Day 253/EW36	Long term extension
Visit 25	E-Day 281/EW40	Long term extension
Visit 26	E-Day 309/EW44	Long term extension
Visit 27	E-Day 337/EW48	Long term extension
Visit 28	E-Day 365/EW52	Long term extension
Visit 29	E-Day 393/EW56	Long term extension
…	…	Long term extension
Visit 778	…	End of treatment in extension phase
Visit 779	28 days after last s.c. dose or 84 days after last LAR dose	End of study

Unlike the above visits that are scheduled to occur after a fixed number of days have elapsed since Day 1, the Visits 777 (End-of-Treatment in core phase) and 778 (End-of-Treatment in extension phase) are scheduled when the patient either completes the respective study phase or decides (or is mandated by the protocol) to prematurely discontinue from the study.

If such a visit happens neither too soon nor too late after the actual last scheduled visit, then it will be mapped to the next scheduled visit that would have occurred had the patient continued in the study. Otherwise, the early discontinuation visit will be mapped to an unscheduled visit.

The 777/778 visit will be considered to have occurred neither too soon nor too late after the actual last scheduled visit if number of days between the two visits is

1. at least half of the planned gap between the patient's actual last scheduled visit and the next scheduled visit and
2. at most the total of
   a. the planned gap between the patient's actual last scheduled visit and the next scheduled visit (that would have occurred if the patient had not discontinued)
   b. half of the planned gap between the patient's next two scheduled visits (that would have occurred if the patient had not discontinued).

If the number of days between the 777/778 visit and last scheduled visit (last scheduled visit +1) is less than the range specified above, then the 777/778 visit will be mapped to an unscheduled visit of the last scheduled visit (last scheduled visit +1); if it's more than the range, then it will be mapped to an unscheduled visit of the last scheduled visit + 1 (last scheduled visit+2).

Further, if a patient continued into the extension phase, then we set Visit 777 in the core phase to Visit 14 without checking the days-in-between. Visit 779 will not be mapped.

2.1.1.4   Conversion of duration in days to duration in months/years

Duration in months = 12 * (Duration in days)/365.25

Duration in years = (Duration in days)/365.25

2.1.1.5   Method for calculating confidence interval

Two-sided 95% confidence intervals for proportions will be calculated using the exact (Clopper-Pearson) method, unless stated otherwise.

Two-sided 95% confidence intervals for change and percentage change from baseline will assume normally distributed data and will be calculated using the t-distribution.

2.1.1.6   Diabetic status

Patients will be assigned a diabetic status at baseline, and at subseuqent visits during the study.

Diabetic status is defined as one of

- Diabetic: Patients taking antidiabetic medication, or prior history of DM, or HbA1c>= 6.5%, or at two different visits FPG>= 126 mg/dL

- Pre-diabetic: Patients not qualifying as diabetic and with 100 mg/dL <=FPG and/ or 5.7% <=HbA1c< 6.5%

- Normal glucose tolerance: Patients not qualifying as diabetic or pre-diabetic and with FPG< 100 mg/dL and/ or HbA1c< 5.7%

Patients classified as diabetic will stay in that category for the rest of the study.

2.2   Analysis sets

Randomized analysis set

The Randomized Analysis Set (RAS) comprises all patients who received at least one dose of pasireotide and have been assigned to either incretin based therapy or insulin by randomization. According to the ITT principle, patients will be analyzed according to the treatment they have been assigned to during the randomization procedure. RAS will be used for the primary analysis and some secondary analyses.

Full analysis set

The Full Analysis Set (FAS) comprises all patients who receive at least one dose of pasireotide. The anti-diabetic treatment group will follow the Intent-To-Treat (ITT) principle. RAS is a subgroup of FAS.

Safety analysis set

The Safety Analysis Set (SAS) includes all patients who received at least one dose of pasireotide and had at least one post-baseline safety assessment. SAS will be used for safety summaries. Randomized patients within SAS will be analyzed according to the anti-diabetic study treatment first received.

The statement that a patient had no adverse events (on the Adverse Event CRF) constitutes a safety assessment. Patients who have received at least one dose of study drug but who have no post-treatment safety data of any kind would be excluded from the SAS.

The analysis sets used for various analyses are summarized in the following table

	RAS	FAS	SAS
Patient Disposition		X	
Protocol Deviation		X	
Demography and baseline disease characteristics		X	
Medical History		X	
Prior Medication		X	
Concomitant Medications			X
Exposure to study medication			X
Primary efficacy analyses	X		
Other efficacy analyses	X	X	
Safety analyses			X

2.3 Patient disposition, demographics and other baseline characteristics

Frequency distributions or summary statistics of data pertaining to subject disposition, demographics, baseline characteristics, medical history, prior medications and protocol deviations will be tabulated and displayed for all enrolled patients.

2.3.1 Patient disposition

Patient disposition will be summarized using the FAS by disease and the 5 treatment groups, i.e., incretin based therapy, insulin, and the three non-randomized treatment groups. Counts of the following items will be included in disposition summaries. Patients who are ongoing in the extension phase will also be summarized.

- Patients treated
  - Treatment ongoing*
  - End of treatment
- Primary reason for end of treatment in the core phase**
- Patients completed core phase
  - Patients did not enter extension phase
  - Entered extension phase
    - Completed extension phase
    - Discontinued in extension, with reasons for discontinuation

* ongoing is only summarized at the time of the data cut-off, if applicable

** core phase is 16 weeks for non-randomized patients, and up to 32 weeks for randomized patients

2.3.2   Demography and baseline disease characteristics

Summary statistics will be provided for demographics, and baseline characteristics using FAS by disease and the 5 treatment groups, i.e., incretin based therapy, insulin, and the three non-randomized treatment groups. Categorical data will be presented by frequencies and percentages. Continuous data will be summarized by mean, standard deviation, minimum, median, and maximum. All data for background and demographic variables, as well as medical history, current medical conditions, results of lab screens, and any other relevant information will also be presented in listing.

2.3.3   Medical history and current medical conditions

Relevant medical history and current medical conditions will be summarized and listed by disease and the 5 treatment groups, i.e., incretin based therapy, insulin, and the three non-randomized treatment groups. The summary will be presented for FAS by primary system organ class (SOC) and preferred term (PT).

2.3.4   Protocol deviations (PDs)

Protocol deviation criteria are specified in the Validation and Planning (VAP) document Module 3. The number and percentage of FAS patients with protocol deviations will be provided for PDs by the end of the study.

All protocol deviations up to data cutoff will be listed by disease and 3 treatment groups, i.e., incretin based therapy, insulin, and non-randomized treatment group.

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

2.4.1 Exposure to Study Treatment

The duration of exposure to the study drug will be summarized by descriptive statistics using the SAS. Exposure will be summarized for pasireotide s.c., pasireotide long-acting, metformin, insulin, sitagliptin, and liraglutide. Exposure to pasireotide will be summarized for all patients. Exposure to metformin will be summarized by the randomized treatment groups (incretin based therapy and insulin), and for the three non-randomized groups. Exposure to all other anti-diabetic medications will be summarized by the two randomized groups.

Duration of exposure of daily dose for those medications that are administered daily (i.e. all anti-diabetic medication and pasireotide s.c.) is calculated as

Duration of exposure (months) = (min (last date of study medication, date of death, date of data cut-off) – first date of study medication + 1)/(365.25/12)

Duration of exposure of pasireotide long-acting is calculated as

Duration of exposure (months) = (min (last date of study medication + 27, date of death, date of data cut-off) – first date of study medication + 1)/ (365.25/12)

2.4.2 Concomitant medication

Concomitant medications and significant non-drug therapies prior to and after the start of the study drug will be summarized and listed by disease and 5 treatment groups (incretin based therapy, insulin, and the 3 non-randomized treatment groups) according to the Anatomical Therapeutic Chemical (ATC) classification system and preferred term by means of frequency counts and percentages using the SAS.

2.5 Analysis of the primary objective

The primary objective is to evaluate the effect of initial treatment with incretin based therapy vs. insulin on glycemic control in patients with Cushing's disease or acromegaly who develop or worsen hyperglycemia on pasireotide, and cannot be controlled by metformin alone or other background anti-diabetic treatments. The primary endpoint will be assessed at the Core EOP.

2.5.1 Primary endpoint

The primary variable is defined as the change from randomization in HbA1c (unit in %) at the time of assessing primary endpoint in the incretin based therapy arm and insulin arm. For patients who require rescue treatment, the last HbA1c assessment prior to rescue treatment will be used for primary efficacy analysis.

2.5.2 Statistical hypothesis, model, and method of analysis

There is no formal hypothesis testing planned in this study. An estimate of the mean difference of the change from randomization in HbA1c between the two randomized arms will be reported along with 95% confidence interval (CI). Patients will be stratified by their disease and baseline

glycemic status. Variance estimation will be based on the following analysis of variance (ANOVA) model using the two stratification factors as well as treatment as fixed effects. RAS will be used for primary analysis:

Change from baseline in HbA1c = Baseline glycemic status + Disease + Treatment + Error
Disease:

    a. Cushing's disease

    b. Acromegaly

Glycemic status at baseline:

    a. HbA1c < 7 %

    b. HbA1c ≥ 7%

Treatment:

    a. Incretin based therapy group

    b. Insulin group

2.5.3   Handling of missing values/censoring/discontinuations

For patients who discontinued the study or require rescue treatment before the time of assessing primary endpoint, the last HbA1c assessment collected 8 weeks after randomization (and prior to or on the date of start of rescue treatment) will be carried forward for primary efficacy analysis. If the patient discontinued the study or used rescue treatment within 8 weeks after randomization, it will be considered missing for primary analysis.

2.5.4   Supportive analyses

As a supportive analysis, the ANOVA for the primary analysis will be repeated. Following ITT principle, the last available HbA1c assessment during core in each randomized arm will be utilized for analysis regardless of time of early discontinuation or rescue treatment use.

RAS will be used for supportive analysis. Subgroup analysis by disease and baseline HbA1c level may be performed.

In addition, the primary efficacy variable will be analyzed by analysis of covariance (ANCOVA) model with treatment and disease as classification variables and baseline HbA1c as the covariate. The least squares mean ("adjusted mean") of change from randomization for each treatment group and its standard error (SE), the difference between two treatment groups and the associated two-sided 95% CI for the difference will be obtained from the following ANCOVA model.

Change from baseline in HbA1c = intercept + Baseline HbA1c + Disease + Treatment + Error
Disease:

    a. Cushing's disease

    b. Acromegaly

Treatment:

    a. Incretin based therapy group

    b. Insulin group

2.6   Analysis of the key secondary objective

There is no key secondary objective in this study.

2.7   Analysis of secondary efficacy objective(s)

The secondary objectives are to assess the overall effect of anti-diabetic intervention on the glycemic control, as well as the sustainability of glycemic control in the insulin arm and the incretin based therapy arm in patients with Cushing's disease or acromegaly. Subgroup analysis by disease may be performed for change in HbA1c and FGP over time.

2.7.1   Change in HbA1c and FPG to EOP

The change in HbA1c and FPG from baseline to the core EOP in patients who received pasireotide (FAS) will be summarized by treatment group (incretin based therapy, insulin, and the three non-randomized treatment groups) using descriptive statistics. 95% confidence intervals will be provided for the changes from baseline.

2.7.2   Proportion of patients with an increase in HbA1c less than or equal 0.3%

The proportion of patients with an increase from baseline in HbA1c $\leq 0.3\%$ at Core EOP will be summarized for each randomized arm. The corresponding 95% confidence interval will be estimated by exact method.

2.7.3   Change in HbA1c and FPG overtime

The change in HbA1c and FPG from randomization overtime and to the core EOP (only for FPG) will be summarized for each randomized arm. Descriptive statistics as well as 95% confidence intervals will be provided for the changes from baseline. Graphical presentation will also be used for change from randomization overtime in HbA1c and FPG.

2.7.4   Proportion received anti-diabetic rescue therapy

The proportion of patients who received anti-diabetic rescue therapy in the incretin based therapy randomized arm will be summarized. The corresponding 95% confidence interval will be estimated by exact method.

2.7.5   Change in HbA1c category

The change in category of HbA1c until the end of the core and extension phases will be summarized by treatment group (incretin based therapy, insulin, and the three non-randomized treatment groups) using shift tables. The categories used will be

•   HbA1c < 6.5%

• $6.5\% \geq$ HbA1c < 7%

•   HbA1c $\geq 7\%$

2.7.6   Change in diabetic status

The change in diabetic status until the end of the core and extension phases will be summarized for the three non-randomized treatment groups using shift tables. Diabetic status is defined in section 2.1.1.6.

3   Safety analyses

The assessment of safety will be based on the frequency of adverse events (AEs), laboratory values that fall outside the pre-determined ranges, vital signs, as well as ECG, hypoglycemia events, thyroid function test and gallbladder examinations data.

3.1.1   Analysis set and grouping for safety analysis

SAS will be used for safety analysis including both pre-randomized period and randomized treatment period. The 5 distinct groups (the 2 randomized treatment arms and the 3 non-randomized groups) will be used to summarize the safety findings, unless otherwise specified. Disease status (Cushing's disease or acromegaly) will also be used to summarize some safety results as appropriate.

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 pasireotide s.c., and 84 days after last dose of pasireotide long-acting, or the follow-up visit, whichever comes later. On-treatment period can be further divided into pre-randomized period and randomized treatment period as depicted in the visit evaluation schedule in [Table 10-1] of the protocol.

3. Post-treatment period: starting at 28+1 days after last dose of pasireotide s.c., and 84+1 days after last dose of pasireotide long-acting, or the follow-up visit + 1 days whichever comes later.

3.1.2   Adverse events (AEs)

All information obtained on AEs will be displayed by patient.

The number and percentage of subjects with AEs will be tabulated by SOC and PT. A subject with multiple adverse events within a body system is only counted once towards the total of this body system if no change in severity.

3.1.2.1 Coding of AEs

Adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

3.1.2.2 Grading of AEs

AEs will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (http://ctep.cancer.gov/forms/CTCAEv4.pdf).

The CTCAE represents a comprehensive grading system for reporting acute and late effects of cancer treatments. CTCAE v4.03 is graded by definition a 5-point scale generally corresponding to clinical severity (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).

For adverse events for which CTCAE grades are not available, grades 1 – 4 corresponding to the severity of mild, moderate, severe, and life-threatening will be used. CTCAE grade 5 (death) is not used in this study. Information regarding death will be collected in the "Study Phase Completion Evaluation" CRF pages.

3.1.2.3   General rules for AE reporting

AE summaries will include all AEs starting on or after study day 1 (i.e. on or after the day of the first administration of study drug) and ending no later than 28 days after last study treatment for pasireotide s.c. and 84 days for pasireotide long-acting or the follow-up visit, whichever is later. All AEs before data cutoff date will be listed, including those that start before study day 1. AEs starting prior to study day 1 will be identifiable based on the AE start date displayed in the listings.

AEs will be summarized by presenting the number and percentage of patients having at least one AE, and having at least one AE in each body system/primary SOC and for each PT using the most current MedDRA coding available prior to database lock. A subject with multiple occurrences of an AE will be counted only once in the AE category.

Separate AE summaries will be presented by primary SOC, PT, and maximum CTCAE grade. A patient with multiple CTCAE grades for an AE will be summarized under the maximum CTCAE grade recorded for the event. In the summaries presented by grade, all AEs will be pooled regardless of whether they are CTCAE gradable or not. AEs with missing CTCAE grade will be summarized under "missing".

Any information collected (e.g. CTCAE grades, relationship to study drug, action taken etc.) will be listed as appropriate.

3.1.2.4   AE summaries

Summary tables for 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 pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged.

The incidence of treatment-emergent AEs (new or worsening from baseline) will be summarized by SOC and or PT, severity (based on CTCAE version 4.03 grades), type of AE, and relation to study treatment.

The following AE summaries will be produced:
- Adverse events, regardless of study drug relationship, by primary system organ class and preferred term

- Adverse events, regardless of study drug relationship, by primary system organ class, preferred term and maximum CTCAE grade
- Adverse events, regardless of study drug relationship, by preferred term
- Adverse events, regardless of study drug relationship, by preferred term and maximum CTCAE grade
- Deaths, by primary system organ class, and preferred term
- Adverse events, with suspected relationship to study drug, by primary system organ class, preferred term
- Adverse events, with suspected study drug relationship, by primary system organ class, preferred term and maximum CTCAE grade
- Adverse events, with suspected relationship to study drug, by preferred term
- Serious adverse events, regardless of study drug relationship, by primary system organ class and preferred term
- Serious adverse events, with suspected relationship to study drug, by preferred term
- Adverse events leading to study drug discontinuation, regardless of study drug relationship, by primary system organ class and preferred term
- Adverse events leading to study drug discontinuation, with suspected relationship to study drug, by primary system organ class and preferred term
- Adverse events requiring dose adjustment or study-drug interruption, regardless of study drug relationship, by primary system organ class and preferred term
- Adverse events of special interest, regardless of study drug relationship, by group name, severity, 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 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.

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.

3.1.2.5   Adverse events of special interest / grouping of AEs

Groupings of AEs of special interest 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).

An Excel file with the exact composition of the adverse events groupings is available in the CREDI folder "/CREDI Projects/S/SOM230C/Administrative files/CIS (Clinical Information Sciences)/Biostatistics/" which is to be used to map reported adverse events to the adverse events groupings. This file is updated periodically based on review of accumulating trial data. The number of patients with at least one event in each category and each preferred term within category will be reported, and AEs of special interest will also be listed.

3.1.3   Laboratory data

For analyzing laboratory results, data from all sources (central and local laboratories) will be combined. The summaries will include all laboratory assessments up to data cut-off date. All laboratory assessments will be listed. Results will be reported for each visit at which collected in the core, extension, and safety follow-up phases through the last study visit.

Biochemistry, hematology, and urine laboratory data will be presented using

- shift tables using CTC grades (if available), otherwise by normal ranges, to compare baseline to the most extreme post-baseline
- listings flagging values with CTC grades (i.e. greater than 0), and outside of the normal ranges otherwise

All laboratory values will be converted into SI units and the severity grade derived using NCI CTCAE v4.03. Glucose will be presented as mg/dL and will be assessed using the ADA criteria 2010. Insulin may also be presented by US unit.

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

- Number and percentage of patients with worst post-baseline CTC grade (regardless of the baseline status). Each patient will be counted only for the worst grade observed post-baseline
- Number and percentage of patients meeting categorical liver function test criteria, including Hy's Law criteria for liver injury (ALT or AST > 3 x ULN and TBIL >= 2 x ULN and ALP < 2 x ULN). Each patient will be counted only for the worst grade observed post-baseline

The following listings will be produced for the laboratory data:

- Listing of all laboratory data with values flagged to show the corresponding CTC grades and the classifications relative to the laboratory reference ranges
- Listing of notable laboratory abnormalities (i.e. CTC grade 3 or 4 laboratory toxicities).

Laboratory samples that are reported as unreliable (e.g. due to technical malfunction) will be excluded from summary tables. All reported laboratory data will be listed and unreliable values flagged.

3.1.4   Other safety data

3.1.4.1   ECG

Fridericia's formula (QTcF) will be used to calculate the heart rate-corrected QT interval (ms) on the heart rate (HR bpm) and QT (ms) as follows:

$$QTcF \ (ms) = QT \ / \ (RR)^{1/3}$$

The derivation will be used when QTcF is missing. All ECG data (heart rate (bpm), PR interval (ms), QT interval (ms), QRS duration (ms), QTcB interval (ms)) will be listed by patient and visit/time. Abnormalities will be flagged. Summary statistics will be provided at baseline and scheduled post-baseline time points for ECG variables PR, QRS, QT/QTcF interval and ventricular rate. Shift table from baseline to worst on-treatment result and summary statistics of

changes from baseline will also be provided. Number and percentage of patients with clinically notable QT/QTcF interval values will be summarized.

Summary statistics (n, mean, standard deviation, minimum, median, and maximum) will be provided by visit/time for the above parameters. Descriptive statistics will be provided for change from baseline to different time points in heart rate, PR interval, QT interval, QRS duration, and QTcF interval. Shift table based on notable values will be provided for ECGs.

The notable criteria for PR is

- Increase > 25% compared to baseline to a post-baseline value > 200 ms

The notable criteria for QRS is

- Increase > 25% compared to baseline to a post-baseline value > 110 ms

The notable criteria for HR are

- Increase > 25% compared to baseline to a post-baseline value > 100 bpm
- Decrease > 25% compared to baseline to a post-baseline value < 50 bpm

The notable criteria for QT and QTcF are

- an increase from baseline > 30 ms at any post-baseline
- an increase from baseline > 60 ms at any post-baseline

All vital signs data (height (cm), weight (kg), body temperature (°C), supine pulse rate (bpm), and systolic/diastolic blood pressure (mmHg)) will be listed by patient and visit/time, and abnormalities will be flagged on listing. Shift table based on notable value will be provided for vital signs.

The criteria for clinically notable abnormalities are defined as follows:

Clinically notable elevated values

- Systolic BP: $\geq$ 180 mmHg and an increase $\geq$ 20 mmHg from baseline
- Diastolic BP: $\geq$ 105 mmHg and an increase $\geq$ 15 mmHg from baseline.
- Supine pulse: $\geq$ 120 bpm with increase from baseline $\geq$ 15 bpm

Clinically notable below normal values

- Systolic BP: $\leq$ 90 mmHg and a decrease $\geq$ 20 mmHg from baseline
- Diastolic BP: $\leq$ 50 mmHg and a decrease $\geq$ 15 mmHg from baseline
- Supine pulse: $\leq$ 50 bpm with decrease from baseline $\geq$ 15 bpm

3.1.4.2   Hypoglycemia events

The number of treatment emergent hypoglycemia events, as well as the number of patients with hypoglycemia events will be summarized for SAS by disease and 5 treatment groups. Hypoglycemia events will be defined based on CTCAE grade.

3.1.4.3   Thyroid function tests

Change from baseline to different time points for thyroid function tests including Free T4 and TSH will be summarized along with corresponding descriptive statistics.

3.1.4.4   Gallbladder examinations

Shift table of baseline to worst on-treatment result for gallbladder examinations will be provided.

3.2   PD and PK/PD analyses

Not applicable

3.3   Patient-reported outcomes

Not applicable

3.4   Biomarkers

Not applicable

3.5   Other Exploratory analyses

Not applicable

3.6   Interim analysis

Not applicable

4   Sample size calculation

4.1   Primary analysis

There is no formal hypothesis testing planned in this study.

A total sample size of 68 randomized evaluable patients (in 1:1 allocation ratio to incretin based therapy and insulin) with at least 8 weeks of randomized treatment without any rescue anti-diabetic medication is required. In order to reach 68 randomized evaluable patients, approximately 79 patients will be randomized based on current drop-out/rescue rate prior to Week 8 (i.e., patients without 8 weeks of randomized treatment or took rescue medication prior to Week 8). The total number of enrolled patients will be based on the actual randomization (which occurs within 16 weeks after patients are enrolled) rate which will be monitored regularly.

The sample size was calculated to ensure that the half-width of the 95% confidence interval around the mean difference of the change from randomization to Week 16 (the subsequent scheduled visit after 16 weeks in randomization) in HbA1c (%) will be approximately 0.5%. The calculation was performed using R version 3.00 and based on a standard deviation of 1.03%, which was consistent with the results from the CSOM230B2305 phase III trial.

5   Change to protocol specified analyses

Two additional secondary efficacy objectives have been added to the table of study objectives in section 1.3, with the details given in the newly added sections 2.7.5 and 2.7.6. These two analyses have been added to allow more detailed description of the glycemic control in study patients.Appendix

5.1   Imputation rules

Partial dates will remain partial in the data listing. For the purpose of analysis, the following imputation rules will be used to impute the partial dates: if the day and month is missing, it will be replaced by 30th June (to be used only for prior events, e.g. medical history); if only the day is missing it will be replaced by the 15th of that month. For the dates known to be within the trial period, if this imputation make the date later then the trial completion date, use the trial completion date; if the imputed date is earlier then the first medication date, use the first medication date.

The imputation of partial date for AE and concomitant medication will follow Novartis standard rules (See Programming Datasets Specifications (PDS) for details).