CSOM230B2410

Non-interventional study for the generation of long term safety and efficacy data of pasireotide s.c. in patients with Cushing's disease (Post- Authorization Safety Study)

Statistical Analysis Plan

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Date	Version	Summary of Changes
11 January 2016	2.0 Am. 5	First Version
21 January 2021	2.1	Change of sponsor Reformatting according with SOP 06BM13R02
22 September 2023	2.2	Update for final clinical study report

Approval Page

Document Title: **Non-interventional study for the generation of long term safety and efficacy data of pasireotide s.c. in patients with Cushing's disease (Post-Authorization Safety Study)**
Version 2.2

Prepared and Approved by:

Name (Title)	Signature	Date

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Contents

1 LIST OF ABBREVIATIONS

AE	Adverse event
AESI	Adverse Event of Special Interest
ACTH	Adrenocorticotropic Hormone
ATC	Anatomical Therapeutic Classification
CM	Concomitant Medication
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
IFC	Informed Consent
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NCI	National Cancer Institute
PT	Preferred Term
QoL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TFLs	Tables, Figures, Listings
UFC	Urinary Free Cortisol
ULN	Upper Limit Normal
VAS	Visual Analogic Scale
WHO	World Health Organization

2 INTRODUCTION

This statistical analysis plan (SAP) describes all planned analyses for the clinical study report (CSR) of study CSOM230B2410 , a Non-interventional study for the generation of long term safety and efficacy data of pasireotide s.c. in patients with Cushing's disease (Post-Authorization Safety Study).

2.1 CLINICAL OBJECTIVES

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

2.2 STATISTICAL DESIGN / MODEL

This is a multi-center, non-interventional study for the generation of long term safety and efficacy data of pasireotide s.c. in patients with Cushing's disease (Post- Authorization Safety Study).

2.2.1 Interim analyses

Interim analyses have been requested by Health Authorities and will be performed every year until study end, with the first analysis done 12 months after study start.

The final analysis will occur when all patients complete the study. Due to the expected small number of patients enrolled during the first 12 months after study start, the first interim analysis will only include summaries of demographics, patient disposition, and duration of exposure, and lists of deaths (if any), serious adverse events, adverse events, and laboratory data. For the subsequent interim analyses, the following tables/listings will be provided:

Tables

- Patient disposition (FAS)
- Analysis set
- Demographics and baseline data (FAS)
- Relevant medical history and current medical conditions by primary system organ class and preferred terms (Safety Set)
- Duration of exposure to study drug (Safety Set)
- Shift tables of biochemistry and hematology using CTC grades from baseline to the worst post-baseline value (Safety Set)
- Adverse events regardless of relationship with pasireotide s.c. by primary system organ class, preferred term (Safety Set)
- Adverse events regardless of relationship with pasireotide s.c. by preferred term (Safety Set)
- Adverse events regardless of relationship with pasireotide s.c. by primary system organ class, preferred term, maximum severity (Safety Set)
- Deaths by primary system organ class, preferred term (Safety Set)
- Serious adverse events regardless of relationship with pasireotide s.c. by primary system organ class, preferred term (Safety Set)
- Adverse events leading to study drug discontinuation, regardless of relationship with pasireotide s.c. by primary system organ class, preferred term (Safety Set)
- Adverse events with suspected relationship to pasireotide s.c. by primary system organ class, preferred term (Safety Set)
- Findings of the gallbladder imaging (presence of gallstones, presence of sludge, dilatation of ductal system, thickening)

Listings

- Deaths (Safety Set)
- Serious adverse events (Safety Set)
- Adverse events leading to study drug discontinuation (Safety Set)
- Study completion (FAS)
- Patient demographics (FAS)
- Dose administration record (FAS)
- Adverse events (FAS)
- Laboratory values by patient (biochemistry/hematology)

Note that further outputs may be added as considered necessary.

2.3 STATISTICAL SOFTWARE

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

3 CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Not applicable.

4 STATISTICAL METHODS

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

4.1 Data analysis general information

Data will be summarized and displayed by time intervals based visit windows rather than by a strict visit schedule.

Patients who discontinue treatment prior to the 3-year observation period, will have their safety and efficacy parameters reported according to the time window that corresponds to Day of last dose of pasireotide s.c. plus 90 days.

Continuous variables will be summarized by number of patients, mean, standard deviation, minimum, median and maximum. Categorical variables will be summarized by absolute and relative frequencies. Counts of missing values for both continuous and categorical variables will be reported.

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

Data will be analyzed according to the data analysis Section 6 of the study protocol (as amended on 20SEP2013) which is available in Appendix 16.1.1 of the CSR. Details are given in the following sections and more technical details are provided, as applicable, in Appendix 16.1.9 of the CSR. It is planned that the data from all study sites that participate in this study will be pooled, so that an adequate number of patients will be available for analysis.

Interim analyses will be performed every year as requested by Health Authorities. The first analysis will be conducted about 12 months after the first patient enters the study. After this first analysis there will be one interim analysis on a yearly basis. The recruitment period is expected to be approximately 8 years and each enrolled patient will be followed up for 3 years after enrollment. The final analysis will occur when all patients have completed the study. The same analysis will be performed at all analysis time points.

For each analysis a cut-off date will be set. All data collected up to this cut-off date will be included in the analysis.

Any data collected beyond the cut-off date for an analysis will not be included in the analysis. Only data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. For example, if the cut-off date is 15 June 2010 then an AE starting on 13 June 2010 will be reported, whereas an AE with start date on 17 June 2010 will not be reported.

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

Incomplete start dates of adverse events and concomitant medications will be imputed according to the conventions, as described in section 5. The imputed start date will be used for the comparison with the cut-off date.

If it is required to impute an end date to be able to perform a specific analysis (e.g. end date after the cut-off date) the cut-off date needs to be imputed as an end date (to allow for calculation of treatment exposure duration and dose intensity for instance).

4.1.1 Groupings for analysis

Based on prior pasireotide s.c. use, two patient cohorts will be distinguished:

- Cohort 1: patients who started pasireotide s.c. at the time of study entry (on or after the signing of the informed consent)
- Cohort 2: patients who started pasireotide s.c. prior to study entry

Most of the efficacy and safety analyses will be done by these cohorts, in addition to the analysis for the overall population. Furthermore, if the cohort of patients with prior pasireotide s.c. use is heterogeneous and if the number of patients is sufficient, selected safety and efficacy analyses will be done for subgroups of this cohort where the subgrouping will be based on the duration of prior pasireotide s.c. use. Subgroups will be defined and justified by the Clinical Trial Team after review of the distribution of the duration of prior pasireotide s.c. use.

If there is a sufficiently large number of patients treated with a specific combination therapy, there might be a separate analysis for this subgroup of patients:

- patients treated with monotherapy pasireotide s.c.
- patients treated with combination with other therapies

Number of patients in each analysis set will also be summarized by cohort and overall as well as for the subgroup from German sites.

4.2 Patient disposition, demographics and other baseline characteristics

4.2.1 Patient disposition

Frequency distributions will be used to summarize the patient disposition at the time of analysis (treatment ongoing, treatment completed, treatment discontinued prematurely, study ongoing, study completed, study discontinued prematurely) and associated reasons for discontinuation of study medication and study using the FAS and the subgroup of patients from German sites. The follow-up time, i.e. the patient's time in the study (in months), will be summarized with descriptive statistics.

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 last prior pituitary surgery/irradiation, duration of prior treatment with pasireotide, baseline symptoms), will be summarized using descriptive statistics and will be listed as required. This summary will be prepared for the FAS and the subgroup of patients from German sites.

The duration of prior treatment with pasireotide (in months) will be summarized with descriptive statistics, as continuous variable and by category (<=3 months, >3 to 6 months, >6 to 12 months, >12 months). The number and percentage of patients who used pasireotide as single therapy and of those who used it as combination therapy will be presented. This summary will be prepared for the FAS and the subgroup of patients from German sites.

4.2.2 Patient demographics and other baseline characteristics

Demographic data (such as age, sex, race, ethnicity, height, weight), disease characteristics, and other baseline characteristics will be summarized descriptively overall and by cohort using the FAS and the subgroup of patients from German sites.

Qualitative variables (e.g. gender) will be summarized by means of contingency tables. Quantitative variables (i.e. age, weight) will be summarized by appropriate descriptive statistics.

4.2.3 Medical History

Medical history and ongoing conditions (also including history of smoking, history of alcohol use, presence of hepatitis B and C infection) will be summarized by cohort and listed. 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.

4.2.4 Prior medication for Cushing’s disease

Prior medication for Cushing's disease will be summarized by preferred term, overall and by cohort. This summary will be prepared for the FAS and the subgroup of patients from German sites.

4.2.5 Prior and concomitant therapy

Prior and concomitant medications and significant non-drug therapies will be listed and summarized by cohort in the safety set.

Medications will be classified as prior or concomitant based on the following rules and will be coded using the WHO Drug Reference List (WHO DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (WHO ATC) classification system:

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

The number and percentage of patients with prior and concomitant medications will be presented separately by ATC class and preferred term according to the WHO DRL dictionary.

5 HANDLING OF MISSING DATA AND OUTLIERS

5.1 AE date imputation

Partial adverse event start dates are imputed with reference to the treatment start date. Completely missing start dates will not be imputed.

Any missing onset date, causality, or severity must be queried for resolution. Unsolved missing values will be imputed according to the following:

AE start date imputation:

1. If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
2. If the AE start date year value is less than the treatment start date year value, the AE started before treatment. Therefore:
    a. If AE month is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).
    b. Else if AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).
3. If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore:
    a. If the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).
    b. Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).
4. If the AE start date year value is equal to the treatment start date year value:
    a. And the AE month is missing the imputed AE start date is set to the AE reference start date + 1 day.
    b. Else if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).
    c. Else if the AE month is equal to the treatment start date month or greater than the treatment start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

AE end date imputation:

1. If the AE end date month is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, 31DECYYYY, date of death).
2. If the AE end date day is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, last day of the month, date of death).
3. If AE year is missing or AE is ongoing, the end date will not be imputed.

If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date.

5.2 Concomitant medication date imputation

Partial concomitant medication start dates are imputed with reference to the treatment start date as outlined below.

Completely missing start dates will not be imputed.

Any missing date will be queried for resolution. For any unsolved missing dates, the following rules in the following order will be applied to decide if a concomitant medication or a significant non-drug therapy was taken after the start of the study treatment and to decide if the data should be included in the summary table. Originally collected date will be listed in listings.

CM start date imputation:

1. If the CM start date year value is missing, the imputed CM start date is set to one day prior to treatment start date.
2. If the CM start date year value is less than the treatment start date year value, the CM started before treatment. Therefore:
    a. If the CM month is missing, the imputed CM start date is set to the mid-year point (01JulYYYY).
    b. Else if the CM month is not missing, the imputed CM start date is set to the mid-month point (15MONYYYY).
3. If the CM start date year value is greater than the treatment start date year value, the CM started after treatment. Therefore:
    a. If the CM month is missing, the imputed CM start date is set to the year start point (01JanYYYY).
    b. Else if the CM month is not missing, the imputed CM start date is set to the month start point (01MONYYYY).
4. If the CM start date year value is equal to the treatment start date year value:
    a. And the CM month is missing or the CM month is equal to the treatment start date month, then the imputed CM start date is set to one day prior treatment start date.
    b. Else if the CM month is less than the treatment start date month, the imputed CM start date is set to the mid-month point (15MONYYYY).
    c. Else if the CM month is greater than the treatment start date month, the imputed CM start date is set to the month start point (01MONYYYY).

CM end date imputation:

1. If CM end day is missing and CM month/year are non-missing then impute CM day as the minimum of treatment end date and the last day of the month.
2. If CM end day/month are missing and CM year is non-missing then impute CM day as the minimum of treatment end date and the end of the year (31DECYYYY).
3. If CM day/month/year is missing then use the treatment end date + 1 day as the imputed CM end date.
4. If imputed CM end date is less than the CM start date, use the CM start date as the imputed CM end date.

If complete (imputed) CM end date is available and the imputed CM start date is greater than the (imputed) CM end date, then imputed CM start date should be set to the (imputed) CM end date.

6 VARIABLES AND ENDPOINTS

6.1 DERIVATION RULES

6.1.1 AEs coding/grading

AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

If CTCAE grading does not exist for an AE, grades 1 to 4 corresponding to the severity of mild, moderate, severe, and life-threatening will be used. The CTC/severity grade will not be imputed if missing. CTC grade 5 (death) will not be used because the outcome of an AE is not recorded on the AE CRF pages.

6.1.2 Study drug start and end date

Treatment start date for cohort 1: defined as the first date at which a non-zero dose of pasireotide s.c. was administered during the study and recorded on the DAR (e)CRF.

Treatment start date for cohort 2: defined as the first date at which a non-zero dose of pasireotide s.c. was administered prior to study entry and recorded on the CMD (e)CRF.

Treatment end date (same for the 2 cohorts) (The date of last administration of study drug) is defined as the last date at which a non-zero dose of study drug was administered and recorded on the DAR (e)CRF. If the end of the last dosing period with a non-zero dose is missing, the "last known date patient took study drug" (as reported on the completion panel (CMP)) will be used.

Date of first dose after informed consent (IFC): defined as the first date at which a non-zero dose of pasireotide s.c. was administered during the study (i.e. after IFC) and recorded on the DAR (e)CRF.

If treatment with pasireotide s.c. is still ongoing at the time of data cut-off for analysis (i.e. no end date on DAR and CMP (e)CRF), it will be assumed that treatment was ongoing until the last contact date (see Section 6.1.4).

Periods with a specific dose of study medication may have incomplete start and/or end dates (e.g. FEB2015 to MAR2015), however, it is assumed that month and year are always known. If the day is missing in the start date,

- the 15th of the respective month is used for imputation, if not before the end date of the previous period,
- the day after the previous end date is used otherwise.

After imputation of start dates, incomplete end dates are imputed. The unknown end date is set

- to one day before the next start date if the known month and year are equal to month and year of the next start - 1 day
- to the last day of the known month otherwise.

6.1.3 Calculation of "time since prior event" variables

All "time since prior event" variables (e.g. time since diagnosis) will be calculated relative to the date of first dose in the study:

time since prior event (in days) = date of first dose - date of prior event.

If the "time since prior event" variable is reported in months, the result will be divided by 30.4375 (= 365.25/12).

If the date of the prior event is incomplete, the missing parts will be imputed:

- by the first day of the month if only the day is missing
- by the first day of the year (i.e., 01Jan) if day and month are missing.

6.1.4 Last contact date

The last contact date is defined as the latest date among the following:

- All assessment dates (e.g. vital signs assessment dates, dates at which questionnaires were completed, imaging dates, dates at which blood samples were taken, ECG dates, etc.)
- Medication dates including study medication and concomitant medications
- AEs start and end dates
- Last known date patient took study drug as reported on the completion panel

If any of the dates for the above measurements are partial dates, the earliest possible date will be used to impute the date (i.e. first day of month if month and year are known, first day of year if only the year is known).

If the last contact date is after the date of death, the last contact date will be set to the date of death.

6.1.5 Study day

Study days are calculated relative to the date of first dose during the study. The date of first dose defines Day 1. Day -1 is one day before Day 1, Day -2 two days before Day 1, Day 2 one day after Day 1, and so on. That is, there is no Day 0.

More specifically, the study day is calculated as

study day = (date of assessment/event - date of first dose) + 1

if the assessment or event is on or after the date of first dose, and as

study day = (date of assessment/event - date of first dose)

otherwise.

6.1.6 Baseline definition

The last non-missing assessment before or on the day of the patient's first dose during the study is considered the baseline assessment.

If no assessment is available before or on the day of first dose, the missing assessment may be imputed by the earliest post-dose assessment, provided it was performed within a pre-defined time window after first dose and before end of treatment.

Time windows depend on the type of assessment; they are displayed in Table 6-1. Baseline values assessed after first dose will not be used as post-baseline assessments.

Table 6-1 Time window for baseline assessments (only for cohort 2)

Type of assessment	Time window after first dose (1)
Vital signs	0 day
ECG	1 week
Pituitary imaging	6 months
Gallbladder imaging	6 months
Quality of Life questionnaires	6 months
Assessment of clinical symptoms of Cushing's disease	1 week
Salivary cortisol	1 week
Blood sample for efficacy parameters (serum cortisol, ACTH, lipids)	1 week
Blood sample for safety tests (hematology, blood chemistry, hormones)	0 days
24-hour urine collection for UFC determination	1 week

(1) Assessments performed during this time window after first dose are accepted as bas assessment if no assessment was performed before or on the day of the first dose.

6.1.7 Time windows

There is no visit schedule and no planned assessment in this non-interventional study. Assessment related data are collected as they become available during the study period. Therefore assessments are assigned to time windows based on the study day on which the assessment is performed. For mean UFC, the sample day of the first urine sample included in the calculation of mean UFC will be used for assignment to time windows.

If there are multiple values within a time window, the assessment closest to the target day of the time window will be used, if not indicated otherwise. If two assessments are equally close (e.g. 7 days before and 7 days after target day), the later will be used.

Time windows will be assigned according to the window schema in Table 6-2 if assessments are expected more frequently than every 6 months. Otherwise the time windows in Table 6-3 will be applied (e.g., for tumor volume, variables related to patient reported outcome questionnaires, findings of gallbladder ultrasound).

Table 6-2 Time windows

Window name (1)	Window No.	Target Day	Starting Day of Window	Ending Day of Window
Baseline	1	-	-	1 (2)
Month 1	2	30	2	60
Month 3	3	91	61	136
Month 6	4	183	137	229
Month 9	5	275	230	320
Month 12	6	365	321	458
Month 18	7	550	459	641
Month 24	8	731	642	821
Month 30	9	914	822	1005
Month 36	10	1096	1006	1187
After Month 36	11	-	1188	No upper limit
Last value on treatment		DLD (3)	2	DLD + gap (4)
Day 90 after last dose		DLD + 90 days	DLD+gap+1 days	DLD + 90 days

(1) Windows are named according to their target days. For example, the target day for window Month 6 is 6 * 30.4375 days, where 30.4375 is the standard length of a month (=365.25/12). The starting day of the window is the midpoint between target day of previous window and current window and the ending day is the midpoint between target day of current window and next window.
Note that only post-baseline on-treatment assessments are assigned to windows Month 1, Month 2, etc., up to 'after Month 36'.

(2) For some parameters, the earliest assessment after first dose is used as baseline assessment if no assessment is available before or on the day of first dose. This assessment is then exclusively used as baseline assessment although is falls into a post-baseline window.

(3) DLD = Day of last dose of pasireotide s.c.

(4) gap = number of days after DLD during which assessments and events are considered on-treatment. gap=3 for efficacy analyses, gap=28 for safety analyses

Table 6-3 Time windows for analyses of tumor volume, patient reported outcome variables and gallbladder ultrasound

Window name (1)	Window No.	Target Day	Starting Day of Window	Ending Day of Window
Baseline	1	-	-	1 (2)
Month 6	4	183	137	320
Month 12	6	365	321	458
Month 18	7	550	459	641
Month 24	8	731	642	821
Month 30	9	914	822	1005
Month 36	10	1096	1006	1187
After Month 36	11	-	1188	No upper limit
Last value on treatment		DLD (3)	2	DLD + gap (4)
Day 90 after last dose		DLD + 90 days	DLD+gap+1 days	DLD + 90 days

(1) Windows are named according to their target days. For example, the target day for window Month 6 is 6 * 30.4375 days, where 30.4375 is the standard length of a month (=365.25/12). The starting day of the window is the midpoint between target day of previous window and current window and the ending day is the midpoint between target day of current window and next window.
Note that only post-baseline on-treatment assessments are assigned to windows Month 6, Month 12, etc., up to 'after Month 36'.

(2) For some parameters, the earliest assessment after first dose is used as baseline assessment if no assessment is available before or on the day of first dose. This assessment is then exclusively used as baseline assessment although is falls into a post-baseline window.

(3) DLD = Day of last dose of pasireotide s.c.

(4) gap = number of days after DLD during which assessments and events are considered on-treatment. gap=3 for efficacy analyses, gap=28 for safety analyses

6.1.8 Quality of life

Cushing QoL questionnaire

Completion of nine or more items of the 12-item Cushing QoL questionnaire is required for it to be considered evaluable for that assessment. If there are more than 3 items missing at an assessment, the total score will be set to missing (i.e., no more than 25% missing items). Standardized scores are calculated as follows:

First raw scores are obtained as the sum of the ratings on all QoL questions for a single patient Table 6-4 shows the ratings for each answer of the QoL questionnaire.

Table 6-4 Cushing QoL Questionnaire 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

Then the standardized score, Y, is calculated for each patient as Y = 100 * (X - n)/(n*5 - n*1) = 100 * (X - n)/4*n

where X denotes the raw score and n the number of questions answered by the patient.

The higher the score, the better the QoL. The best possible standardized score is 100, and the worst possible standardized score is 0.

EQ-5D Health Questionnaire

The EQ-5D-3L consists of 2 pages – the EQ-5D-3L descriptive system and the EQ visual analogue scale. The descriptive system comprises the same 5 dimensions as the EQ--5D-3L (mobility, self care, usual activities, pain/discomfort, anxiety/depression). However, each dimension now has 3 levels: no problems, some problems and problems.

Health state classification will be converted to utility scores, during data analysis stage, based on a list representing the EQ-5D value set for the UK using the time trade-off method. This list has 243 values for all possible EuroQoL health states. For example, a health state of 11111 will have a score of 1.00 and a health status of 12132 will have a score of 0.089. If at least one of the five items is missing, the utility score will be set to missing.

The list representing the EQ-5D value set for the UK is based on a regression model and the following worked example indicates how these coefficients are to be used so as to compute the estimated values for each state (Table 6-5).

Table 6-5 EQ-5D preference weight scoring system

EuroQoL dimension	Level 2	Level 3
Mobility	0.069	0.314
Self-care	0.104	0.214
Usual activity	0.036	0.094
Pain / discomfort	0.123	0.386
Anxiety / depression	0.071	0.236
	Constant = 0.081 subtract for any state different from (1 1 1	N3 = 0.269 subtract for any state with at least one level 3

The arithmetic needed to recover the estimated value for any health state from this table of decrements is given by the following example:

- Taking health state 1 1 2 2 3
- Full health (1 1 1 1 1) = 1.0
- Constant term (for any dysfunctional state)(subtract 0.081)
- Mobility.. level 1(subtract 0)
- Self-care.. level 1(subtract 0)
- Usual activity.. level 2(subtract 0.036)
- Pain / discomfort.. level 2(subtract 0.123)
- Anxiety / depression.. level 3(subtract 0.236)

- Level 3 occurs within at least 1 dimension (subtract N3 parameter 0.269)
- Hence the estimated value for state 1 1 2 2 3 is given by
- 1.0 - 0.081 - 0.036 - 0.123 - 0.236 - 0.269 = .255

The EQ VAS records the respondent's self-rated health on a 20 cm vertical, visual analogue scale with endpoints labeled 'the best health you can imagine' and 'the worst health you can imagine'. This information can be used as a quantitative measure of health as judged by the individual respondents.

6.2 SAS procedures used for inferential analysis computation

6.2.1 Exact Clopper-Pearson confidence limits for a proportion

The SAS® procedure PROC FREQ will be used to determine proportions and the associated exact Clopper-Pearson 95% CI. The following SAS code will be used:

PROC FREQ DATA=xxx;

<BY cohort;>

TABLES binvar /BINOMIAL OUT=prop; OUTPUT OUT=yyy BINOMIAL;

RUN;

Here 'cohort' denotes a classification variable which identifies the cohorts, and 'binvar' denotes the binary variable for which the proportion and CI is calculated. 'binvar' must be coded such that the relevant level is the lowest level because the confidence interval is only calculated for this level. Get _BIN_ (binomial proportion), XL_BIN, and XU_BIN (lower and upper limit of CI) from output dataset yyy, merge it with the relevant level from dataset prop, and compare _BIN_ and PERCENT (must be identical) to make sure that the correct level was selected.

6.2.2 Distribution-free confidence interval for median

The SAS® procedure PROC UNIVARIATE will be used to calculate distribution-free confidence intervals based on order statistics. The following SAS code will be used:

ODS OUTPUT Quantiles=quant;

PROC UNIVARIATE DATA=xxx CIPCTLDF;

<BY cohort;> VAR numvar RUN;

Here 'cohort' denotes a classification variable which identifies the cohorts, and 'numvar' denotes the numerical variable for which the CI is calculated. Among other variables, the output dataset quant includes estimates (variable ESTIMATE), and lower and upper confidence limits (variables LCLDISTF and UCLDISTF) for various quantiles including the median (QUANTILE ='50% Median').

6.2.3 Mixed model for repeated measures

The following SAS code will be used to fit the mixed model for repeated measures.

```
proc mixed;
   class patient window ;
   model outcome = window base /ddfm=kr;
   repeated window /patient = patient type=un;
   lsmeans window / cl;
run;
```

Here, `patient` denotes the patient identifier (e.g. SID1A), `window` the time window assigned, `outcome` the outcome variable (e.g. mean UFC), and `base` the corresponding baseline value.

6.2.4 Confidence intervals for occurrence rates of AEs and SAEs

The occurrences of AE or SAE by preferred term will be modeled to follow approximately a Poisson process with constant intensity θ. The rate parameter θ will be estimated as λ=D/T, where

- Numerator (Di) = total number of events (AE or SAEs by PT) observed within the cohorts and overall (i=1,2,3 for cohort 1, 2 and overall, respectively). PTs which were reported more than once on the same day (within the same patient) will be counted as one event under the highest severity grade.
- Denominator (Ti) = The sum of exposure time t across all patients in group i per 100 patient years. For a single patient the exposure time t is derived as: t = (minimum date of (last dose + 28 days, last contact day, analysis cutoff day) - date of first dose during study+ 1) /365.25. The sum of the exposure time of all patients in group i will be divided by 100 to obtain the exposure time per 100 patient years.
- Note: the analyses of safety and tolerability assessments will concentrate on the on-treatment period, defined to be the period from Day 1 to 28 days after last dose of pasireotide s.c. i.e. the exposure period for Ti is accordingly adjusted.

Conditionally on T, an exact 100*(1-α)% confidence interval for a Poisson variable with parameter θ*T and observed value D can be obtained based on (Garwood, 1936), from which an exact 100*(1-α)% confidence interval for D/T will be derived as follows (Sahai, 1993; Ulm, 1990):

Lower confidence limit $L = \frac{0.5c_{\alpha/2,2D}}{T}$ (in SAS: (0.5*cinv(alpha/2,2*D(i))/T(i))

Upper confidence limit $U = \frac{0.5c_{1-\alpha/2,2D+2}}{T}$ (in SAS: (0.5*cinv(1-.05/2, 2* D(i)+2)/ T(i)) for i=1,2,3 and D(i) >0 and 0 otherwise,

where $c_{\alpha,k}$ is the αth quantile of the Chi-square distribution with k degrees of freedom.

Garwood, F. 1936. Fiducial limits for the Poisson distribution. Biometrika. 28(3/4):437-442

Ulm, K. 1990. A simple method to calculate the confidence interval of a standardized mortality ratio. American Journal of Epidemiology 131(2):373-375.

Sahai, H. and Khurshid, A. (1993a). "Confidence intervals for the mean of a Poisson distribution: A review", BiomtrcJ, 35, 857-867.

Sahai, H. and Khurshid, A. (1993b). "Confidence intervals for the ratio of two Poisson means", MathScntst, 18, 43-50.

7 ANALYSIS POPULATIONS

7.1 RELEVANT PROTOCOL DEVIATIONS

The number and percentage of patients in the FAS with any protocol deviation will be tabulated by the deviation category (as specified in Attachment 9.1) and cohort.

All protocol deviations will be listed.

7.2 DEFINITION OF POPULATIONS FOR ANALYSIS

7.2.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients who have signed informed consent (or acknowledged an equivalent document) and have been treated with pasireotide s.c. after enrollment into the study.

The full analysis set will be used for all efficacy analyses.

7.2.2 Safety Set

The safety set consists of all patients who have signed informed consent (or acknowledged an equivalent document), have been treated with pasireotide s.c. after enrollment into the study, and have at least one safety assessment after the first dose.

Patients who do not fulfill these criteria will be identified before database lock and presented in a listing.

The safety set will be used for all safety analyses.

8 PLANNED ANALYSES

As described in Section 4.1, analyses will be performed every year with the first analysis conducted approximately 12 months after the first patient entered the study.

8.1 Analysis of the primary efficacy objective

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

8.1.1 Primary efficacy endpoint

There is no primary efficacy endpoint in this study.

8.1.2 Statistical hypothesis, model, and method of analysis

The sample size for this study is not based on statistical considerations. It is anticipated that up to approximately 100 sites in about 35 countries will participate in the study. The study will enroll a minimum of 100 patients up to a maximum of 200 patients. The actual sample size may differ from this planned number.

8.2 Analysis of secondary efficacy objective(s)

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

8.2.1 Secondary efficacy endpoints

The secondary efficacy endpoints are as follows:

1. Proportion of patients with a mean UFC ≤ ULN at 1, 3, 6, 12, 24 and 36 months after enrollment into the study.
2. The absolute and percentage change from baseline in biochemical measures of disease activity (mean UFC, serum cortisol, serum cortisol after dexamethasone, salivary cortisol, ACTH, fasting serum lipid profile (total cholesterol, HDL, LDL)) over time.
3. Proportion of patients achieving normalization of biochemical measures of disease activity (serum cortisol, serum cortisol after dexamethasone, salivary cortisol, ACTH) over time, where normalization refers to being within the upper and lower limit of normal ranges.
4. The absolute and percentage change from baseline in clinical signs and symptoms (blood pressure, body weight, body mass index, waist circumference) over time.
5. The proportion of patients with favorable shift from baseline in clinical symptoms of Cushing's disease over time.
6. The change from the last dose of pasireotide s.c. to 90 days after permanent discontinuation of pasireotide s.c. for patients who discontinue pasireotide s.c. prior to completing 3-year observation period. This change will be evaluated for all available continuous efficacy parameters.
7. The absolute and percentage change from baseline in tumor size over time.
8. The absolute and percentage change from baseline in patient reported outcome questionnaires (Cushing QoL and EURO QoL) over time.

All efficacy analyses will be done for all patients in the FAS and for the two cohorts. And all efficacy analyses except those under 5 will be done for the subgroup patients from German sites. Additionally, the efficacy analyses described under 1, 2, and 3 above will be repeated for the following subgroups of patients:

- Patients treated with monotherapy pasireotide s.c. throughout the study
- Patients treated with a combination of pasireotide s.c. with any other therapy for Cushing's disease throughout the study
- Patients who switched from monotherapy to combination therapy or vice versa at any time during the study

For all continuous efficacy variables (biochemical measures of disease activity, blood pressure, body weight, body mass index, waist circumference, tumor size), a Mixed Effects Repeated Measures Model will also be employed to assess the longitudinal changes in these variables.

Except for the analysis of change from end of treatment to 90 days later, the efficacy analyses will only consider on-treatment values, defined as values assessed before end of treatment + 3 days.

All assessments will be assigned to time windows based on the study day on which the assessment was performed. If there are multiple values within a time window, the assessment closest to the target day of the time window will be used, if not indicated otherwise. Further details including the start and end days of the time windows are available in Appendix 16.1.9 of the CSR.

The continuous efficacy parameters will be also evaluated through a couple of sensitivity analyses: the first will be imputing the worst value at that time window in case of missing data and the second on the patients with the full set of values. The same Mixed Model will be employed for both the analyses.

8.2.1.1 *Proportion of patients with mean UFC ≤ ULN*

Analysis of all patients

In general, UFC is determined by collecting two or three 24-hour urine samples and calculating the mean of the 24-hour UFC values. However, routinely some sites may also use only one single 24-hour urine sample to assess UFC. Therefore in this study, mean UFC (mUFC) refers to the mean if more than one 24-hour UFC value was reported within 2 weeks and to the single value if only one value was reported.

If a 24-hour urine collection was performed but 24-hour UFC was not documented, 24-hour UFC will be calculated as product of 'urinary cortisol, random' (concentration of cortisol in 24-hour urine) and the total volume of 24-hour urine, if available.

For each time window (Month 1, 3, 6, 9, 12, 18, 24, 30 and 36), the number and proportion of patients with mean UFC (mUFC) ≤ ULN will be presented together with corresponding exact (Clopper-Pearson) 95% confidence intervals (CI) for the proportions. The proportion will be calculated relative to the number of patients with a value for the respective time point (mUFC and ULN).

In addition, the number of patients without mUFC value and the number of patients with missing ULN (but mUFC value available) will be displayed by time window. In each time window, only those patients will be included who were treated during that window and followed up until the end of the respective time window.

Analysis of patients who discontinued pasireotide s.c.

A similar analysis will be performed for the subgroup of patients who discontinued pasireotide s.c. prematurely and had an assessment on-treatment and 90 days after last dose. The statistics described above will be displayed for the patient's last value on treatment and for the last value assessed during the 90 days after last dose. Furthermore, the status of the last mUFC value on treatment (≤ ULN, > ULN) will be cross-tabulated against the status 90 days after last dose.

8.2.1.2 *Absolute and percentage change from baseline in biochemical measures of disease activity*

For each time window (Month 1, 3, 6, 9, 12, 18, 24, 30, 36), observed values and, the absolute and percentage change from baseline in biochemical measures of disease activity (mean UFC, serum cortisol, serum cortisol after dexamethasone, salivary cortisol, ACTH, fasting serum lipid profile (total cholesterol, HDL, LDL) will be summarized with descriptive statistics. Distribution-free 95% CIs will be given for the median changes.

Furthermore, the time course of these parameters will be displayed graphically using box-plots.

In addition, the absolute and percentage change from the last assessment while on pasireotide s.c. to the last value during the 90-days follow-up period will be summarized in a similar manner.

8.2.1.3 *Proportion of patients with normalization of biochemical measures of disease activity*

This analysis will be done for serum cortisol, serum cortisol after dexamethasone, salivary cortisol, ACTH.

For each time window, the number and percentage of patients with normalization of biochemical measures of disease activity will be presented together with corresponding exact

(Clopper-Pearson) 95% CI. For this analysis, a patient is considered to have achieved normalization within a time window if all measurements taken within this window are within the normal range. The proportion will be calculated relative to the number of patients with a value for the respective time point.

8.2.1.4 *Absolute and percentage change from baseline in clinical signs and symptoms*

For each time window, the absolute and percentage change from baseline in clinical signs and symptoms (blood pressure, body weight, body mass index, waist circumference) will be summarized with descriptive statistics. Distribution-free 95% CIs will be given for the median changes.

In addition, the absolute and percentage change from the last assessment while on pasireotide s.c. to the last value during the 90-days follow-up period will be summarized in a similar manner.

8.2.1.5 *Proportion of patients with favorable shift from baseline in clinical symptoms of Cushing's disease*

The clinical symptoms of Cushing's disease (facial rubor, striae, bruising, supraclavicular fat pad, dorsal fat pad) are assessed on a 4-point scale ranging from 0 (none) to 3 (severe). A favorable shift corresponds to a decrease on this scale.

For each clinical symptom of Cushing's disease, the change in clinical symptoms will be analyzed using shift tables: for each time point, the post-baseline result will be cross-tabulated against the baseline result. The number and percentage of patients with a favorable shift from baseline to each time window will be presented together with corresponding exact (Clopper- Pearson) 95% CI.

8.2.1.6 *Absolute and percentage change from baseline in tumor size*

For time windows Month 6, 12, 18, 24, 30, and 36, absolute and percentage change from baseline in tumor volume will be summarized with descriptive statistics. Distribution-free 95% CIs will be given for the median changes. This summary will only include post-baseline evaluations for which the same method of evaluation (CT scan or MRI) as at baseline.

In addition, the absolute and percentage change from the last assessment while on pasireotide

s.c. to the last value during the 90 days after drug discontinuation will be summarized in a similar manner.

8.2.1.7 Absolute and percentage change from baseline in patient-reported outcomes (Cushing QoL and EURO QoL)

Cushing QoL Questionnaire

Completion of nine or more items of the 12-item CushingQoL questionnaire is required for it to be considered evaluable for that assessment. A higher score is indicative of better patient quality of life. The best possible standardized score is 100, and the worst possible standardized score is 0.

The standardized score for the CushingQoL and its absolute and percentage change from baseline will be summarized with descriptive statistics for time windows Month 6, 12, 18, 24, 30, and 36. Distribution-free 95% CIs will be given for the median changes.

The calculation of the standardized score is described in Appendix 16.1.9, Section 4.3.1.1.

EQ-5D-3L Questionnaire

Responses to the EQ-5D will be summarized into a single index, in accordance with the user manual for EQ-5D-3L. The higher the index the better the patient's health state.

The EQ-5D visual analogue scale (VAS) records the respondent's self-rated health on a 20 cm vertical, visual analogue scale with endpoints labeled 'the best health you can imagine' and 'the worst health you can imagine'. This information can be used as a quantitative measure of health as judged by the individual respondent.

For time windows Month 6, 12, 18, 24, 30, and 36:

- the index for EQ-5D questionnaire and its absolute change from baseline will be summarized with descriptive statistics. Distribution-free 95% CIs will be given for the median changes.
- the result from the EQ VAS scale and its absolute and percentage change from baseline will be summarized with descriptive statistics. Distribution-free 95% CIs will be given for the median changes.

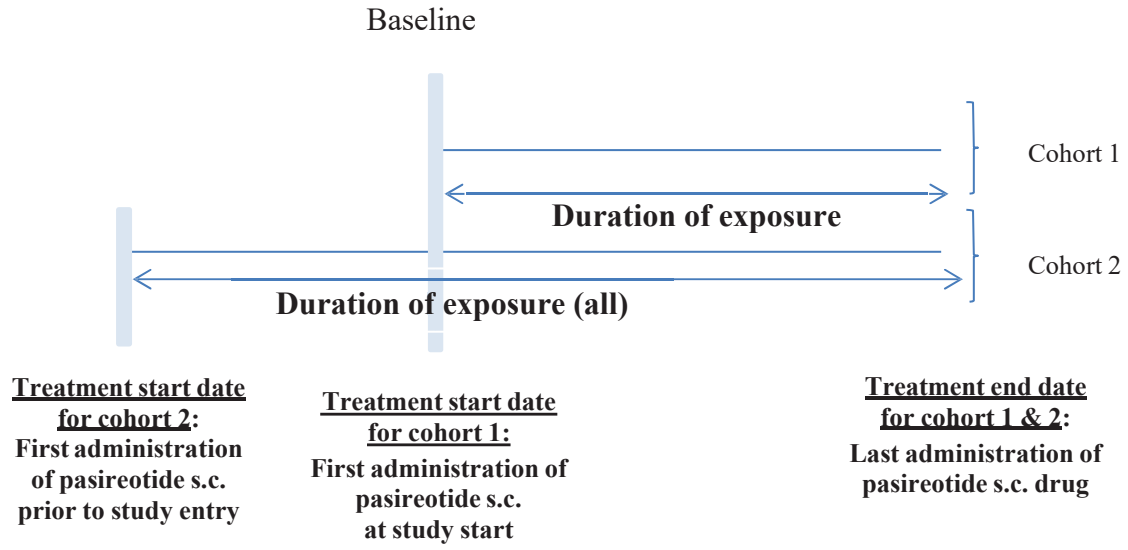
The calculation of the index is described in Appendix 16.1.9, Section 4.3.1.1.

8.3 EXTENT OF EXPOSURE

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

Duration of exposure will be summarized by appropriate descriptive statistics for each cohort.

Figure 8-1 Treatment start and duration of exposure in Cohorts 1 and 2



The following definitions will be used:

Treatment start date for cohort 1: defined as the first date at which a non-zero dose of pasireotide s.c. was administered during the study and recorded on the DAR (e)CRF.

Treatment start date for cohort 2: defined as the first date at which a non-zero dose of pasireotide s.c. was administered prior to study entry and recorded on the CMD (e)CRF.

Treatment end date (same for the 2 cohorts): defined as the last date at which a non-zero dose of study drug was administered and recorded on the DAR (e)CRF. If the end date of the last dosing period with a non-zero dose is missing, the "last known date patient took study drug" (as reported on the completion panel) will be used.

Duration of exposure will be calculated for each cohort separately as the number of days from the treatment start date to the treatment end date, which are defined for the two cohorts above, including days with interruptions.

duration of exposure = treatment end date – treatment start date + 1

The derivation of treatment start and end date is described in Appendix 16.1.9 of the CSR, Section 4.2.1.

Duration of on-study exposure will be calculated as the number of days from the date of first dose after informed consent (IFC) to the treatment end date, including days with interruptions.

duration of on study exposure = treatment end date – date of first dose after IFC + 1

The derivation of treatment start and end date is described in Appendix 16.1.9 of the CSR, Section 4.2.1.

Actual mean daily dose or actual dose intensity of pasireotide s.c. 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, duration of on-study exposure and actual dose intensity while in the study will be summarized with descriptive statistics by cohorts. In addition, a frequency table will show the number and percentage of patients per duration of exposure category (<=1 month, >1 to 3 months, >3 to 6 months, >6 to 12 months, >12 to 24 months, >24 to 36 months,

>36 months). This summary will be prepared for the safety set and the subgroup of patients from German sites.

The number and percentage of patients who used pasireotide as single therapy, who used it as combination therapy, and who switched from single to combination therapy (or vice versa) will be presented by time period (Day 1 to Day 30, Day 1 to Day 91, Day 1 to 183, etc). Each summary of a time period will only include patients who still received pasireotide s.c. at the end of the time period. Patients will be split up into the three groups based on the following definitions:

- Patients are considered to be on single therapy throughout a period if they did not receive any other medication than pasireotide for Cushing's disease during this period.
- Patients are considered to be on combination therapy throughout a period if they received pasireotide in combination with other medications for Cushing's disease throughout this period. Interruptions of less than 10 days are not considered a switch to single therapy.

- Patients who switched from single to combination therapy or vice versa are patients who do not fulfill the condition for single therapy and combination therapy throughout the period, as outlined above.
-

The frequency of dose changes will be classified as 'no change', 1, 2, 3, >3 changes. Similar classifications will be done for dose increases and dose reductions (including interruptions). The frequencies will be summarized by time window (see Table 6-2 in Section 6.1.7), overall and by reason.

8.4 SAFETY ANALYSIS

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

The analyses of safety and tolerability assessments will concentrate on the on-treatment period, defined to be the period from Day 1 to 28 days after last dose of pasireotide s.c. Post- treatment events and assessments (i.e. events and assessments started or performed after the on-treatment period) will be analyzed. In particular, the change between on-treatment period and the period from 28 days after last dose of pasireotide to 90 days after discontinuing pasireotide s.c. treatment will be investigated for continuous parameters in patients who permanently discontinue pasireotide s.c. prior to completing the 3-year observation period.

All safety analyses will be based on the safety set and summarized overall and by cohort. Baseline is described in Section 6.1.6

8.4.1 Adverse events (AEs)

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

The number and percentage of patients reporting any AE will be summarized by primary SOC and PT. AEs and Serious Adverse Events (SAEs) will be reported and collected from patient's enrollment into the study until 28 days after the last dose of pasireotide s.c. at the patient's last follow-up visit. AEs and SAEs will be collected until 90 days after the last dose for patients who permanently discontinue pasireotide s.c. prior to completing 3 years of treatment.

The primary endpoint of this study is the percentage of patients having any pasireotide s.c.- related AEs and SAEs during the 3-year observation period. Pasireotide s.c.-related AEs are AEs for which the investigator suspected a relationship with pasireotide s.c.

AEs that started or worsened during the on-treatment period are called treatment-emergent AEs.

The incidence of treatment-emergent AEs will be summarized by system organ class (SOC), preferred term (PT) and severity. 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, overall and by cohort:

- AEs regardless of relationship with pasireotide s.c. (additionally by country). This summary (> 5% in all patients) will also be prepared for the subgroup of patients from German sites
- AEs suspected to be related to pasireotide s.c.
- SAEs regardless of relationship with pasireotide s.c. (additionally by country)
- Deaths
- AEs leading to study drug discontinuation, regardless of relationship with pasireotide s.c. (restricted to patients with primary reason for discontinuation documented as AEs or abnormal laboratory values)
- AEs leading to study drug discontinuation, suspected to be related to pasireotide s.c. (restricted to patients with primary reason for discontinuation documented as AEs or abnormal laboratory values)
- AEs requiring dose adjustment or study-drug interruption, regardless of relationship with pasireotide s.c.
- AEs requiring additional therapy, regardless of with pasireotide s.c.
- Adverse events of special interest, regardless of relationship with pasireotide s.c.

Post-treatment AEs and post-treatment SAEs will be summarized by primary SOC, PT and maximum CTC grade in patients who discontinued pasireotide s.c. prior to completing the 3- year observation period.

In addition, (S)AEs leading to study discontinuation will be listed. Note that there is no respective flag on the eCRF. Therefore the listings will show all (S)AEs which were ongoing at the time of study discontinuation due to AE or which ended the day before.

Also summary on clinically notable AEs (patients who had grade 3/4 AEs, SAEs, AEs leading to discontinuation or other significant AEs) will be prepared for the subgroup of patients from German sites.

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 project defined group. The specific groupings of AEs as defined in the Attachment 9.2 AESI List (latest documentation available prior to database lock) will be used.

The following tables will be produced:

- AEs of special interest, regardless of relationship with pasireotide s.c., by category, preferred term and maximum CTC grade,
- SAEs of special interest, regardless of relationship with pasireotide s.c., by category, preferred term and maximum CTC grade,
- AEs of special interest, regardless of relationship with pasireotide s.c., by type (any AE, AE suspected to be related to pasireotide s.c., SAE, AE leading to discontinuation, AE requiring dose adjustment or study-drug interruption) and PT

- AEs of special interest, regardless of relationship with pasireotide s.c., by time interval of onset (0 to < 3 months, 3 to < 6 months, 6 to <9 months, etc.), category and preferred term.

Occurrences of AEs and SAEs adjusted for exposure

The exposure times by cohort is different, therefore, exposure adjusted occurrence rates will aid in the interpretation of differences in the occurrence of AEs/SAEs. Exposure adjusted occurrence rates will be presented (per 100 years of patient exposure), together with 95% confidence intervals. Summaries will be presented for treatment emergent AEs and SAEs.

Confidence intervals will be derived assuming a Poisson process for the occurrence of AEs (SAEs). See Section 5.4 for further details.

Summaries of exposure adjusted occurrence rates will be produced for AEs and SAEs by PT. Only AEs (SAEs) with more than 2 occurrences per preferred term will be displayed.

The analyses on occurrences of AEs and SAEs will be repeated by country.

8.4.2 Laboratory evaluation

All laboratory values will be converted into SI units.

Laboratory data will be classified (by biostatistics/SAS programming) into CTC grades according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) v3.0. A severity grade of 0 will be assigned when the value is within normal limits. 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 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):

- Shift tables using CTC grades to compare baseline to the worst post-baseline value
- Shift tables using CTC grades to compare the last post-baseline grade on treatment to the worst grade during the 90 days after permanent discontinuation of pasireotide s.c., in patients who discontinued pasireotide s.c. prematurely.
- For laboratory parameters where CTC grades are not defined, shift tables to the minimum and maximum post-baseline value using the low/normal/high classifications based on laboratory reference ranges.

Patients with laboratory values outside the laboratory reference 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.

HbA1c values will be classified into categories <5.7%, >=5.7% -<6.5% >=6.5% - 8% and >=8%, and categories cross-tabulated in shift tables (baseline versus worst post-baseline category).

A similar analysis will be performed for fasting glucose, classified into categories <100 mg/dL,>=100-<126 mg/dL,>=126 mg/dL (baseline versus worst post-baseline category).

The analyses of glucose will only include patients who were fasting at the time of blood sampling.

8.4.3 Vital signs and weight

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.

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: ≥39.1°C
  ≤35°C
- Weight: Increase from baseline of ≥10%
  decrease from baseline of ≥10%

The following summaries will be produced for each parameter for which notable abnormalities are defined:

- Frequency table of notable values assessed on treatment after baseline
- Shift table comparing the last post-baseline value on treatment to the worst value (i.e. highest value and lowest value) during the 90 days after permanent discontinuation of pasireotide s.c., in patients who discontinued pasireotide s.c. prematurely.

Furthermore for body temperature and sitting pulse, absolute and percentage change from baseline will be summarized with descriptive statistics by time window. Similar summaries were done for blood pressure, weight and waist circumference as part of the efficacy analyses.

8.4.4 ECG

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 for each time window,
- Summary statistics of changes from baseline for each time window,
- Listing of ECG data .

Number (%) of patients with a notable QT interval, based on both QTcB and QTcF will be summarized by cohort at any time post-baseline. ECG shift table based on notable values will be summarized by treatment group. Notable criteria for QTcB/QTcF include:

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

Patients with notable QT interval values or any clinically significant ECG abnormality will be flagged in the listings.

Above analyses will be performed for patients who discontinued pasireotide s.c. prematurely comparing the last post-baseline value on treatment to the worst value during the 90 days after permanent discontinuation of pasireotide s.c.

8.4.5 Gallbladder ultrasound

The findings of the gallbladder imaging (presence of gallstones, presence of sludge, dilatation of ductal system, thickening) will be summarized using frequency tables by time window (Month 6, 12, 18, 24, 30, and 36) and shift tables. In the shift tables, the last post-baseline result on treatment will be tabulated against the baseline result.

9 ATTACHMENTS

9.1 PROTOCOL DEVIATION LIST

Protocol Deviation ID	**Description used to Report PDs to HA/IRBs**
I01	Written informed consent or equivalent document not signed
I02	Patient aged less than 18 years
I03	Patients with no confirmed diagnosis of Cushing's disease
I04	Patients with diagnosis of Cushing's disease for whom surgery has not failed
I05	Patients with Cushing's syndrome for whom surgery is an option
I06	Patient started pasireotide s.c. after the first study visit
E01	Patient with ectopic ACTH-dependent Cushing's syndrome
E02	Patient with adrenal Cushing's syndrome
E03	Patient with Pseudo Cushing's syndrome
G01	Informed consent not appropriately obtained
G02	SAE not reported within 24 hours of awareness

9.2 AESI LIST

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

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

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

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

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

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

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