

Clinical Development

SOM230 (Pasireotide)

Protocol CSOM230B2411 / NCT01915303

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

Authors

[REDACTED]

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**Table of contents**

Table of contents .....	2
List of appendices .....	5
List of figures .....	5
List of tables .....	5
List of abbreviations .....	6
Glossary of terms .....	8
Amendment 4 (12-Jul-2017) .....	9
Amendment 3 (25-Jul-2016) .....	10
Amendment 2 .....	12
Amendment 1 .....	15
Protocol summary: .....	18
1 Background .....	23
1.1 Overview of disease pathogenesis, epidemiology and current treatment .....	23
1.2 Introduction to investigational treatment(s) and other study treatment(s) .....	24
1.2.1 Overview of Pasireotide .....	24
1.2.2 Overview of Cabergoline .....	29
2 Rationale .....	30
2.1 Study rationale and purpose .....	30
2.2 Rationale for the study design .....	31
2.3 Rationale for dose and regimen selection .....	32
3 Objectives and endpoints .....	33
4 Study design .....	35
4.1 Description of study design .....	35
5 Patient population .....	37
5.1 Key inclusion criteria .....	37
5.2 Exclusion criteria .....	39
6 Treatment .....	40
6.1 Patient numbering, treatment assignment .....	40
6.2 Study treatment .....	40
6.2.1 Dosing regimen .....	41
6.2.2 Treatment duration .....	42
6.3 Study drug .....	42
6.3.1 Supply, preparation and storage .....	42
6.3.2 Pasireotide .....	42
6.3.3 Cabergoline .....	42

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6.3.4	Study drug compliance.....	42
6.4	Guidelines for dose modifications and titrations .....	43
6.4.1	Pasireotide and cabergoline dose modification steps.....	43
6.5	Special safety .....	46
6.5.1	Hyperglycemia .....	46
6.5.2	Self-monitoring of blood glucose.....	46
6.5.3	QT prolongation .....	48
6.5.4	Hepatic Safety Management .....	49
6.6	Treatment interruption and treatment discontinuation .....	51
6.7	Permitted concomitant therapy requiring caution and/or action.....	52
6.7.1	Prohibited concomitant therapy .....	53
7	Study flow and visit schedule.....	53
7.1	Study flow and visit schedule .....	53
7.1.1	Screening.....	59
7.1.2	End of treatment, including premature withdrawal and study discontinuation visit .....	60
7.2	Assessment types .....	61
7.2.1	Efficacy assessments .....	61
7.2.2	Safety and tolerability assessments .....	64
8	Safety monitoring and reporting.....	67
8.1	Adverse events .....	67
8.1.1	Definitions and reporting .....	67
8.1.2	Adverse events of special interest .....	68
8.1.3	Laboratory test abnormalities .....	68
8.2	Serious adverse events .....	68
8.2.1	Definitions .....	68
8.2.2	Reporting .....	69
8.3	Pregnancies .....	70
8.4	Warnings and precautions.....	70
8.5	Steering committee .....	70
9	Data collection and management.....	71
9.1	Data confidentiality .....	71
9.2	Site monitoring .....	71
9.3	Data collection .....	72
9.4	Database management and quality control .....	72
10	Statistical methods and data analysis .....	73

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10.1	Analysis sets .....	73
10.1.1	Full Analysis Set .....	73
10.1.2	Safety Set .....	73
10.1.3	Per-Protocol Set .....	73
10.2	Patient demographics/other baseline characteristics .....	73
10.2.1	Treatments (study treatment, concomitant therapies, compliance).....	73
10.2.2	Primary objective .....	74
10.2.3	Handling of missing values/censoring/discontinuations.....	74
10.2.4	Supportive analyses.....	74
10.3	Secondary objectives .....	74
10.3.1	Safety objectives .....	76
		78
10.4	Interim analysis.....	78
10.5	Sample size calculation.....	79
11	Ethical considerations and administrative procedures .....	79
11.1	Regulatory and ethical compliance.....	79
11.2	Responsibilities of the investigator and IRB/IEC/REB .....	79
11.3	Informed consent procedures.....	79
11.4	Discontinuation of the study .....	80
11.4.1	Communication and Publication of Clinical Trial Results .....	80
11.5	Study documentation, record keeping and retention of documents.....	81
11.6	Confidentiality of study documents and patient records .....	82
11.7	Audits and inspections .....	82
11.8	Financial disclosures.....	82
12	Protocol adherence .....	82
12.1	Amendments to the protocol.....	82
13	References (available upon request).....	83
14	Appendices .....	85
14.1	Appendix 1 Karnofsky performance status .....	85
14.2	Appendix 2: Cushing's Syndrome Quality of Life Questionnaire .....	86
14.3	Appendix 3 Patient Report Outcome Questionnaire - SF 12 - v2 .....	90
14.4	Appendix 4: Medications known to be associated with QT interval prolongation.....	93
14.5	Appendix 5: Ferriman-Gallwey Score.....	94

## List of appendices

- [Appendix 1](#): Karnofsky Performance Status Scale
- [Appendix 2](#): Cushing's Syndrome Quality of Life Questionnaire
- [Appendix 3](#): Patient Report Outcome Questionnaire - SF 12 - v2
- [Appendix 4](#): Medications known to be associated with QT interval prolongation
- [Appendix 5](#): Ferriman-Gallwey Score

## List of figures

Figure 1-1	Pasireotide structural and molecular formula .....	25
Figure 1-2	Mean (+/- SE) urinary free cortisol (nmol/24h) at time points up to Month 12 by randomized dose group (Full analysis set - study B2305).....	28
Figure 1-3	Cabergoline structure and molecular formular .....	29
Figure 4-1	Pasireotide-untreated patients at screening .....	35
Figure 4-2	Patients currently treated with maximal tolerated doses of pasireotide monotherapy .....	36
Figure 6-1	Fasting Self-Monitoring Blood Glucose guidelines.....	47
Figure 6-2	QT Prolongation monitoring flow chart.....	49
Figure 6-3	LFT Management Algorithm .....	51
Figure 14-1	Ferriman-Gallwey Scoring Diagram.....	95

## List of tables

Table 3-1	Objectives and related endpoints .....	33
Table 6-1	Dose and treatment schedule.....	41
Table 6-2	Pasireotide and cabergoline dose modification steps for pasireotide un-treated patients .....	44
Table 6-3	Pasireotide and cabergoline dose modification steps for patients currently treated with maximal tolerated doses of pasireotide monotherapy.....	46
Table 6-4	Guidelines for treatment of patients experiencing adverse events.....	52
Table 7-1	Core Phase - Visit evaluation schedule.....	54
Table 7-2	Extension Phase - Visit evaluation schedule.....	56
Table 7-3	Extension Phase - Assessment frequencies.....	58
Table 7-4	Central Laboratory parameters collection plan .....	58
Table 10-1	Categorical clinical signs .....	76

## List of abbreviations

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ACTH	Adrenocorticotrophic hormone
ADA	American Diabetes Association
AE	Adverse Event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
b.i.d. (bid or BID)	bis in diem/twice a day
CD	Cushing's disease
CI	Confidence interval
CMO&PS	Chief Medical Office and Patient Safety
CRF/eCRF	Case Report/Record Form; the term CRF can be applied to either electronic or Paper
CRH	Corticotrophin-releasing hormone
CRO	Contract Research Organization
CSR	Clinical study report
EASD	European Association for the Study of Diabetes
ECG	Electrocardiogram
HAV	Hepatitis A virus
HBc	Hepatitis B core
HbsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
hERG	Human ether-a-go-go-related gene
HRQOL/QoL	Health-related quality of life questionnaires
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IPSS	Inferior petrosal sinus sampling
IRB	Institutional Review Board
IVRS	Interactive Voice Response Systems
IWRS/IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
LDL	Low density lipoprotein
LFT	Liver Function Test
LLN	Lower Limit of Normal
MAP	Master Analysis Plan documents project standards in the statistical methods which will be used within the individual clinical trial SAP documentation
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Cell Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDRD	Modification of Diet in Renal Disease
MRI	Magnetic resonance imaging
mUFC	Mean of urinary free Cortisol
NCI-CTCAE v4.03	National Cancer Institute - Common Toxicity Criteria Adverse Events version 4.03
PHI	Protected Health Information
Plasma ACTH	Plasma Adrenocorticotrophic Hormone
PLT	Platelets
PPAR $\gamma$	Peroxisome Proliferator-Activated Receptor gamma
PPS	Pre Protocol Set
PRO	Patient Reported Outcome

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PT	Prothrombin time
PTT	Partial thromboplastin time
q.d. (qd or QD)	queaque die/once a day
QOL	Quality of life
REB	Research Ethics Board
s.c.	Subcutaneous
SAE	Serious Adverse Event
SAP	The Statistical Analysis Plan (SAP) is a regulatory document which provides evidence of preplanned analyses
SmPC (SPC)	Summary of Product Characteristics
SRIFa	Somatostatin Release Inhibiting Factor Analog
SSA	Somatostatin Analog
Sst	Somatostatin receptors
ULN	Upper Limit of Normal
WBC	White blood cells

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## Glossary of terms

Assessment	A procedure used to generate data required by the study
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Patient Number (Patient No. NOVDD) Subject Number (Subject No. NCDS)	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study.
Core phase	The main phase of the study. All patients enrolled to the study will undergo core phase.
Extension phase	If pasireotide is not approved for commercial use or reimbursed in a country, the respective countries patients will go on to extension phase.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Patient number	A number to identify patient. It is 9 – digit number
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Patient group	A treatment group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. Cohorts are not expanded, new cohorts are enrolled.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points.

## **Amendment 4 (12-Jul-2017)**

The main objectives of this protocol amendment are as follows:

- Participating patients currently have the option to continue study treatment if pasireotide is not yet approved for commercial use and/or reimbursed - if country reimbursement is applicable - in each respective country, or until 31st December 2017, whichever occurs first. At the time of this protocol amendment, pasireotide is not yet approved for commercial use and/or reimbursed in several participating countries. In order to continue to provide access to treatment for patients in these countries and to collect longer-term safety and efficacy data, the maximum duration of the extension phase of the study will be extended by two further years, to 31st December 2019. The first results from the interim analysis related to the core phase have become available and support the use of the combination treatment, justifying the continued use of study medication.

All current procedures and collections will still be done.

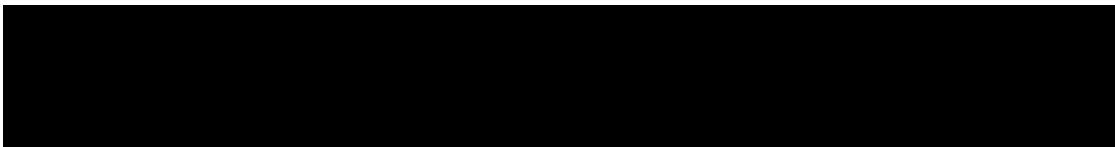
The main changes to the protocol and the sections affected are detailed below:

- List of Abbreviations section: Multiple abbreviations were updated
- Section 4.1, Extension Phase Section was updated to extend the trial until 31Dec2019
- Section 6.2.2, Extension Phase Section was updated to extend the trial until 31Dec2019
- Section 8.2.2, Reporting section was updated to replace Drug Safety & Epidemiology (DS&E) with Chief Medical Office & Patient Safety (CMO&PS)
- Section 8.4, Pregnancy section was updated to replace Drug Safety & Epidemiology (DS&E) with Chief Medical Office & Patient Safety (CMO&PS)
- Multiple grammatical errors corrected throughout

## **IRB/IEC**

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.



## **Amendment 3 (25-Jul-2016)**

**Important note for Spain: The changes noted in Amendment 2 will not be applicable for Spain. Spain will follow all protocol procedures from Amendment 1, in addition to the applicable changes for Amendment 3 (if approved).**

The main objectives of this protocol amendment are as follows:

Participating patients currently have the option to continue study treatment if pasireotide is not yet approved for commercial use and/or reimbursed - if country reimbursement is applicable - in each respective country, or until 31st December 2016, whichever occurs first. At the time of this protocol amendment, pasireotide is not yet approved for commercial use and/or reimbursed in several participating countries. In order to continue to provide access to treatment for patients in these countries and to collect longer-term safety and efficacy data, the maximum duration of the extension phase of the study will be extended by one further year, to 31 December 2017. All current procedures and collections will still be done.

Also, an analysis of this trial will be performed at the end of the core phase of the study, while the analysis related to the overall phase, including the core and the extension phases, will still be performed at the end of the extension phase after December 2017.

Based on continuous review of the sections and assessments that pertain to patient safety the following sections were updated to align with the current standards for patient safety within the pasireotide study program:

- Adverse Events of special interest section 8.5.1 was added.
- The pregnancy section (Section 8.3) was updated to specify duration of follow-up for newborn babies.
- The Hepatic Safety Management section (Section 6.5.4) was updated to include extra safety precautions such as:
  - The inclusion that if any of the noted criterion is observed, the timing of the sponsor notification is changed from 72 to 48 hours.
  - New wording has been added to this section to describe the SAE terminology to be reported if no cause of the Liver Function Test (LFT) abnormalities is identified and is considered medically significant.

Lastly, STEP roll over protocol language has been added, in case continued treatment is necessary.

The main changes to the protocol and the sections affected are detailed below:

- List of Abbreviations section: RAP updated to SAP
- Section 4.1, Extension Phase Section was updated to extend the trial until 31Dec2017 and STEP roll over protocol language added
- Section 6.2.2, Extension Phase Section was updated to extend the trial until 31Dec2017 and STEP roll over protocol language added
- Section 6.5.4, Hepatic Safety Management Section was updated with new standard safety language



- Figure 6-3, Figure was updated with a new LFT Management Algorithm
- Section 7.2.2.5.3, Liver Function Testing section was updated to state if an abnormal liver function criterion is observed; the extra tests should be done within 48 hours, instead of 72 hours.
- Section 8.1.2, Adverse Events of Special Interest section was added
- Section 8.3, Pregnancy section was updated to include the follow up for newborn babies, if applicable
- Section 10, was updated to include wording regarding the two separate analyses that will be done.
- Section 10.3.1.2, Analyzing of Adverse Events of special interest was added
- Section 10, 10.3.1.3 and Section 10.3.2, abbreviation RAP changed to SAP (statistical analysis plan)
- Section 10.4, Interim Analysis section was updated to include wording regarding the interim analysis and clinical study reports that will be done after both the core phase and the core and extension phase combined.

**IRB/IEC**

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## Amendment 2

The main objectives of this protocol amendment are as follows:

1. To combine Group 1 (pasireotide naïve patients) and Group 2 (patients currently treated with maximal tolerated doses of pasireotide monotherapy) into a single cohort of patients. Of the 52 patients hitherto enrolled in the study, 50 belong to Group 1 and 2 patients to Group 2. The enrolment pattern of the trial indicates that primarily pasireotide-naïve patients will be included. Therefore, Groups 1 & 2 will be combined and all patients – both pasireotide-naïve and the ones currently on maximal tolerated dose but not controlled – will enter a 35-week core phase study. All patients will be analyzed in a single cohort. The visit evaluation schedule for both core and extension phases will follow the current Group 1 schedule.
2. As a consequence of merging the two groups of patients into a single one, the trial primary objective and its related endpoints are updated accordingly. The primary objective now reads: "To evaluate the overall efficacy of the treatment regimen of pasireotide alone or in combination with cabergoline in patients with Cushing's disease." The primary endpoint now reads: "Proportion of patients who attain mUFC  $\leq$  1.0xULN at week 35 with pasireotide alone or in combination with cabergoline."
3. The enrolment target of the trial will be reduced from 128 to 64 patients. Assuming that the proportion of patients who attain a mUFC  $\leq$  1.0xULN at week 35 will be 34 %, derived from a weighted mean of the original assumed response rates for Group 1 (35%) and 2 (28%) and assuming that a maximum of 6 out of 64 patients (approx. 10 %) will be enrolled in Group 2, a sample size of 64 will result in a precision of the response of 12.8 % for the associated two-sided 95% CI considering a drop-out rate of 10%.
4. A significant amount of time would be required to enroll 64 patients to Group 2. In order to publish the study results within the originally proposed timeline, it was decided that the trial will conclude when the enrolment is reached at 64 patients.
5. As Group 1 and Group 2 will be combined into one single cohort, Group 1 and Group 2 inclusion criteria will be combined into one single list. No changes will be made to exclusion criteria as it is already one single list for both groups.
6. The duration of screening period will be increased from 21 days to 28 days. Current experience indicates that it takes about 4 weeks to have the investigation performed for study eligibility.

[REDACTED]

[REDACTED]

[REDACTED]

8. There are patients who show high sensitivity to pasireotide and whose UFC levels are decreased to levels below LLN. These patients require pasireotide to be reduced from the starting dose of 0.6 mg bid to 0.3 mg bid; a few of them, despite the dose reduction, require further reductions to 0.3 mg qd in order to maintain normal levels of UFC. As such, the lowest dose of pasireotide allowed for the trial was changed to 0.3mg qd from 0.3mg BID.

[REDACTED]

[REDACTED]

The main changes to the protocol and the section affected are detailed below:

- In the Protocol Summary table, the following sections were updated to reflect all patients to be enrolled to one single group:
  - Primary Objective(s) and Key Secondary Objective
  - Secondary Objectives
  - Study Design
  - Population
  - Inclusion Criteria
  - Other Assessments
- Sections 2.2 - Rationale for the study design and 2.3 - Rationale for dose and regimen selection were updated to combine Group 1 and Group 2 into one single group.
- Section 3 and Table 3-1 Objectives and endpoints were updated. The primary objective was updated; the secondary objectives were updated. The patient populations to be enrolled to the trial were not changed. The primary and secondary analysis will still be performed per patient population, but separately.
- Section 4.1 Description of study design was updated to no longer include two groups of patients. Pasireotide untreated patients at screening and patients currently treated with maximal tolerated doses of pasireotide monotherapy will be enrolled into one single group undergoing the same schedule of events.
- Section 5 Patient population section was revised to no longer have two separate groups of patients.
- Section 5.1 Key inclusion criteria section consisted of two separate lists, one for Group 1 and one for Group 2. The two lists were merged into one inclusion criteria list applicable to all patients. No changes were made to the exclusion criteria.
- Section 6.2 Study treatment was reworded to describe one study treatment procedures for all patients.
- Section 6.2.2 Treatment duration was updated to state that all patients will receive a total of 35 week treatment in the core phase. Treatment duration for the extension phase remains the same.
- Table 6-3 Pasireotide and cabergoline dose modification steps for patients currently treated with maximal tolerated doses of pasireotide monotherapy was further clarified.
- Section 6.6 Treatment interruption and treatment discontinuation was updated to include one single group of patients.
- Section 7.1.1 Screening - The screening period was extended from 21 to 28 days.
- Tables 7-2 and 7-4 were removed. Tables 7-1 and 7-3 were updated to reflect one single group of patients.
- Section 7.2.1.1 Mean urinary free cortisol (mUFC) was updated to reflect one single group of patients.

- Section 10.1 Analysis sets was updated.
- Section 10.2.2 Primary objectives, statistical hypothesis, model and method of analysis was updated to re-word the primary objective to no longer having two groups of patients.
- Section 10.3 Secondary objectives were updated to no longer having two groups of patients.
- Section 10.5 Sample size calculation was updated to no longer having two groups of patients.
- Appendix 5: Ferriman-Gallwey score system descriptions were updated so that they are consistently with the diagrams in Figure 14-1.

**IRB/IEC**

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## Amendment 1

The main objectives of this protocol amendment are as follows:

1. Per Health Authorities recommendations
  1. A urine pregnancy assessment will be performed at every scheduled visit in Core and Extension Phases, as a measure of precaution. All pre-menopausal women who are not surgically sterile will have a urine dip-stick pregnancy test at every scheduled visit. Patients will be required to undergo a serum pregnancy test if a urine dip-stick test is positive.
  2. To align with the ADR profile of cabergoline and pasireotide as described in the approved labels, the following exclusion criteria will be added to the protocol for both Group 1 and Group 2 patients:
    - a. Patients with severe hepatic impairment (Child Pugh C) and hypersensitivity to pasireotide or cabergoline.
    - b. Patients with lung, pericardial, and retroperitoneal fibrosis; gastro-duodenal ulcer or digestive haemorrhage, galactose intolerance, Parkinson's disease, uncontrolled hypertension and Raynaud's syndrome.
    - c. Patients with end-stage renal failure and/or hemodialysis
  3. An estimated glomerular filtration from serum creatinine will be calculated using the traceable Modification of Diet in Renal Disease (MDRD) in order to monitor renal function during the study. This calculation will be performed at screening and at the end of treatment visits for all patients. In adults, the isotope dilution mass spectrometry (IDMS) – traceable Modification of Diet in Renal Disease (MDRD) is considered to be an appropriate equation for estimating glomerular filtration rate from serum creatinine. Therefore, this approach is considered adequate to monitor renal function during the study.
2. The safety monitoring and report section was inadvertently deleted from the original protocol prior to finalization. Therefore, it will be added to the protocol.
3. More restrictive requirements regarding contraception were implemented within the SOM230 clinical development program based on a new internal pregnancy guidance. Pasireotide is not teratogenic but studies in rats and rabbits have shown effects on female reproductive parameters: At 10mg/kg/day in rats, the frequency of early/total absorption and mal-rotated limbs was increased. At 5mg/kg/day in rabbits, increased absorptions, reduced fetal weights and ensuring skeletal variation were observed. As a result, double barrier contraception is required for male participants and had been implemented in the protocol:
  - “Male participants in the trial must agree to use a condom during intercourse, and not to father a child during the study and for the period of 30 days following stopping of the study treatment.”

4. A criterion to exclude pregnant or nursing (lactating) women will be added to be consistent with SOM230 clinical development program standards:
  - “Pregnant or nursing (lactating) women where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5mIU/mL).”
5. Cabergoline dosing time was added in Section 6.3.3. In the same section, the protocol also clarified that Dostinex, a generic form of Cabergoline, will be used for the trial in available participating countries.
6. Two options on how to dispense different dosages of study medication to patients were introduced in Section 6.
7. Additional language was added to Section 7 of the protocol to describe the new enrollment and eligibility confirmation process.
8. The following administrative errors will be corrected in the original protocol. Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

The main changes to the protocol and the section affected are detailed below:

- The following 2 inclusion criteria were left out in the Protocol Summary section for Group 2 inclusion criteria, they were now added:
  - Patients currently treated with maximal tolerated doses of pasireotide for at least 8 weeks at the time of screening but have not achieved biochemical control. These patients will enter the study starting combination therapy.
  - Male or female patients aged 18 years or greater
- List of abbreviations section - mUFC abbreviation was updated from “mean of urinary frequency control” to “mean of urinary free cortisol”
- Figure 4-1 - referenced footnotes above “pasireotide 0.9mg + cabergoline 1.0 mg qd” section were deleted.
- Figure 4-1 - week numbers were added to the bottom of the graph.
- Section 6.1 - Patient numbering, treatment assignment was added.
- Section 6.5.3 - referenced Figure 6-3 was changed to 6-2
- Weight measured at every scheduled visit was added to Table 7-1 through Table 7-4 to be consistent with the protocol text.
- Coagulation and Urinalysis time points were updated in Table 7-3 to be consistent with time points listed in Table 7-5.
- Urinalysis time points were updated in Table 7-4 to be consistent with time points listed in Table 7-5.
- Tissue archival language was deleted in Section 9.3.
- Irrelevant language was deleted from Section 9.4 Database management and quality control.
- Section 10.2.3 Handling of missing values/censoring/discontinuations was reworded.
- Section 10.4 Interim analysis was reworded.

- Section 11.4 Discontinuation of the study, the last sentence was revised to read: “Specific conditions for terminating the study are outlined in Section 7.1.2.1.”
- Figure 14-5 - Ferriman-Gallwey Scoring Diagram was changed to Figure 14-1 Ferriman-Gallwey Scoring Diagram.
- Figure 14-1 - Post Authorization Safety Study (PASS) table was deleted.
- Appendix 4 reference was updated.

**IRB/IEC**

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**Protocol summary:**

<b>Protocol number</b>	CSOM230B2411
<b>Title</b>	A Phase II trial to assess the efficacy and safety of pasireotide s.c. alone or in combination with cabergoline in patients with Cushing's disease
<b>Brief title</b>	Study of the efficacy and safety of pasireotide s.c. +/- cabergoline in patients with Cushing's disease
<b>Sponsor and Clinical Phase</b>	Novartis, Phase II
<b>Investigation type</b>	Drug
<b>Study type</b>	Interventional
<b>Purpose and rationale</b>	Cushing's disease (CD) is a rare debilitating disease. Patients have excessive adrenocorticotrophic hormone (ACTH) secretion from a benign pituitary adenoma, which stimulates the adrenal to produce excess cortisol. The incidence of Cushing's disease ranges from 1-3 patients per million per year. Cushing's disease is associated with severe morbidity and premature mortality. While surgical removal of the adenoma is first line therapy for CD, the success rate of surgery is between 65-90% for microadenomas (tumors < 1cm) with recurrence rates between 10-20% after 10 years. Irradiation of the pituitary is another option but it may take many years to be effective and it is curative in only 15-45% of the cases. When surgery and/or irradiation fail, or for those patients from whom such therapies are not an option, the remaining alternatives are pharmacological treatment or bilateral adrenalectomy. Pasireotide is the first pituitary-targeted medical treatment approved for patients with Cushing's disease. Preliminary data ( <a href="#">Feeelders 2010</a> ) indicate synergic effect between pasireotide and cabergoline in increasing the biochemical control rate in patients. The purpose of this prospective, multicenter, open-label study is to evaluate the efficacy and safety of pasireotide alone or in combination with cabergoline in patients with Cushing's disease as measured by proportion of patients achieving normal UFC at the end of the study period. The study will enroll patients who are pasireotide - untreated at the time of screening and patients who are currently on treatment with maximal tolerated doses of pasireotide but still with uncontrolled mUFC.
<b>Primary Objective(s) and Key Secondary Objective</b>	To evaluate the overall efficacy of the treatment regimen of pasireotide alone or in combination with cabergoline in patients with Cushing's disease.
<b>Secondary Objectives</b>	<ol style="list-style-type: none"> <li>1. To assess the changes in mUFC from baseline to study end at each scheduled visit where UFC is measured</li> <li>2. To assess overall efficacy of pasireotide alone or in combination with cabergoline as measured by normal mUFC levels at each scheduled visit when UFC is measured</li> <li>3. To evaluate overall efficacy of pasireotide alone or in combination with cabergoline as measured by controlled and partially controlled mUFC levels at each scheduled visit when UFC is measured</li> <li>4. To evaluate the duration of controlled or partially controlled mUFC</li> <li>5. To assess the effect on plasma ACTH and serum cortisol</li> <li>6. To assess the effect on the continuous measures of clinical signs of hypercortisolism</li> <li>7. To assess the effect on the categorical measures of clinical signs of hypercortisolism</li> <li>8. To assess the improvement of health-related quality of life</li> <li>9. To evaluate the safety profile of pasireotide alone or in combination with cabergoline</li> </ol>

<b>Study design</b>	<p>The study consists pasireotide-untreated patients at screening and patients currently treated with maximal tolerated doses of pasireotide in two study phases.</p> <p><b>Core Phase</b></p> <p>Pasireotide-untreated patients at screening - this includes patients who have never received pasireotide or patients who have received pasireotide sometime in the past but it was not discontinued because of safety - will start pasireotide at 0.6mg twice a day for 8 weeks. Should biochemical control not be achieved by week 8 and the tolerability of the 0.6mg dose be good, the dose of pasireotide will be increased to 0.9mg twice a day for another 8 weeks. If biochemical control is not achieved with the higher dose of pasireotide, cabergoline at increasing doses will be added, starting at 0.5mg once a day, and then increased to 1.0mg once a day. Dose adjustments for cabergoline due to safety issues are allowed. Patients will be treated for a total of 35 weeks, including three 1-week (+ 3 days) dose titration periods at weeks 8, 17 and 26.</p> <p>Patients currently treated with maximal tolerated doses of pasireotide monotherapy for at least 8 weeks - 0.3mg twice a day, 0.6mg twice a day or 0.9mg twice a day for at least 8 weeks - but still did not achieve biochemical control will add cabergoline 0.5mg once a day at study entry. They will continue the combination treatment for 8 weeks. Should biochemical control not be achieved by week 8, the dose of cabergoline will be increased to 1.0mg once a day and patients will be monitored for another 8 weeks. Dose adjustments for cabergoline due to safety issues are allowed. Patients will also be treated for a total of 35 weeks, including one 1-week (+ 3 days) dose titration period at week 8.</p> <p><b>Extension phase</b></p> <p>After 35 weeks of treatment patients have the option to continue study treatment if pasireotide is not yet approved for commercial use and/or reimbursed - if country reimbursement is applicable - in each respective country. Novartis will have a local transition plan in order to ensure that all trial patients will still have access to the study medication without any delay in their treatment. Patients who discontinue or complete the extension phase are required to complete a study completion visit 28 days (+/- 2 days) after last dose is received in the extension phase.</p>
<b>Population</b>	<p>The study population will consist of patients with persistent or recurrent Cushing's disease or patients with de novo Cushing's disease that are not considered candidates for pituitary surgery (poor surgery candidates, surgically unapproachable tumor, patients with no visible pituitary tumor, patients who refuse surgery). A confirmed Cushing's disease diagnosis is required. The study will enroll a total of 64 patients:</p> <ul style="list-style-type: none"><li>• Patients who are not currently treated with pasireotide, i.e., patients who have never received pasireotide or have received pasireotide in the past and were not discontinued because of safety.</li><li>• Patients who are currently treated with maximal tolerated doses of pasireotide monotherapy for at least 8 weeks at screening, without achieving normal mUFC.</li></ul>

<b>Inclusion criteria</b>	<ol style="list-style-type: none"><li>Written informed consent obtained prior to any screening procedures</li><li>Adult patients with confirmed diagnosis of ACTH-dependent Cushing's disease as evidenced by all of the following:<ol style="list-style-type: none"><li>The mean of three 24-hour urine samples collected within 2 weeks &gt; 1xULN with 2 out of 3 samples &gt;ULN</li><li>Morning plasma ACTH within the normal or above normal range</li><li>Either Magnetic resonance imaging (MRI) confirmation of pituitary adenoma &gt; 6 mm, or inferior petrosal sinus gradient &gt;3 after Corticotrophin-releasing hormone (CRH) stimulation for those patients with a tumor less than or equal to 6 mm*. For patients who have had prior pituitary surgery, histopathology confirming an ACTH staining adenoma</li><li>If IPSS had previously been performed without CRH (e.g. with DDAVP), then a central to peripheral pre-stimulation gradient &gt; 2 is required. If IPSS had not previously been performed, IPSS with CRH stimulation is required. If surgery has been performed and histopathology indicates an ACTH-secreting tumor, there is no need for IPSS even for patients with a tumor &lt; 6mm. If surgery has not been performed and the tumor is &lt; 6mm, IPSS is required to confirm the diagnosis using CRH, or DDAVP if CRH is not available.</li></ol></li><li>Patients with de novo Cushing's disease can be included only if they are not considered candidates for pituitary surgery (e.g. poor surgical candidates, surgically unapproachable tumors, patients who refuse to have surgical treatment)</li><li>Male or female patients aged 18 years or greater</li><li>Karnofsky performance status <math>\geq 60</math> (i.e. requires occasional assistance, but is able to care for most of their personal needs)</li><li>Patients on medical treatment for Cushing's disease the following washout periods must be completed before screening assessments are performed<ul style="list-style-type: none"><li>Inhibitors of steroidogenesis (ketoconazole, metyrapone): 1 week</li><li>Pituitary directed agents: Dopamine agonists (bromocriptine, cabergoline) and Peroxisome Proliferator-Activated Receptor gamma (PPAR<math>\gamma</math>) agonists (rosiglitazone or pioglitazone): 4 weeks</li><li>Octreotide LAR, Lanreotide SR and Lanreotide autogel: 14 weeks</li><li>Octreotide (immediate release formulation): 1 week</li><li>Progesterone receptor antagonist (mifepristone): 4 weeks</li></ul></li><li>Patients can be considered to enter the trial if they meet any <b>one</b> of the following criteria:<ul style="list-style-type: none"><li>They are naïve to pasireotide</li><li>They have received pasireotide in the past and have been discontinued because of lack of efficacy (2 weeks of washout prior to screening for patients treated with pasireotide subcutaneously and 12 weeks of washout prior to screening for patients treated with pasireotide LAR)</li><li>Patients who are on maximal tolerated dose but have not achieved biochemical control</li></ul></li><li>Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, if they are using highly effective methods of contraception during dosing and for 30 days after stopping study medication.</li><li>Male participants in the trial must agree to use a condom during intercourse, and not to father a child during the study and for the period of 30 days following stopping of the study treatment.</li></ol>
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<b>Exclusion criteria</b>	<ol style="list-style-type: none"> <li>Patients with compression of the optic chiasm causing any visual field defect that requires surgical intervention</li> <li>Diabetic patients with poor glycemic control as evidenced by HbA1c &gt;8%</li> <li>Patients with risk factors for torsade de pointes, i.e. patients with a baseline QTcF &gt;450 ms in males, and &gt; 460 ms in females. hypokalemia, hypomagnesaemia, uncontrolled hypothyroidism, family history of long QT syndrome, or concomitant medications known to prolong QT interval.</li> <li>Patients with clinically significant valvular disease.</li> <li>Patients with Cushing's syndrome due to ectopic ACTH secretion</li> <li>Patients with hypercortisolism secondary to adrenal tumors or nodular (primary) bilateral adrenal hyperplasia</li> <li>Patients who have congestive heart failure (NYHA Class III or IV), unstable angina, sustained ventricular tachycardia, clinically significant bradycardia, advanced heart block, history of acute MI less than one year prior to study entry or clinically significant impairment in cardiovascular function</li> <li>Patients with liver disease such as cirrhosis, chronic active hepatitis, or chronic persistent hepatitis, or patients with ALT/AST &gt; 2 X ULN, serum bilirubin &gt;2.0 X ULN</li> <li>Patients with serum creatinine &gt;2.0 X ULN10.</li> <li>Patients with WBC &lt;3 X 10<sup>9</sup>/L; Hb 90% &lt; LLN; PLT &lt;100 X 10<sup>9</sup>/L</li> <li>Patients with severe hepatic impairment (Child Pugh C) and hypersensitivity to pasireotide or cabergoline</li> <li>Patients with lung, pericardial, and retroperitoneal fibrosis; gastro-duodenal ulcer or digestive hemorrhage, galactose intolerance, Parkinson's disease, uncontrolled hypertension and Raynaud's syndrome.</li> <li>Pregnant or nursing (lactating) women where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (&gt; 5 mIU/mL).</li> <li>Patients with end-stage renal failure and/or hemodialysis</li> </ol>
<b>Investigational and reference therapy</b>	Paireotide: subcutaneous; 0.3mg, 0.6mg and 0.9mg twice a day Cabergoline: oral; 0.5mg and 1.0mg once a day
<b>Efficacy assessments</b>	<ul style="list-style-type: none"> <li>Mean urinary free cortisol (mUFC)</li> <li>Serum cortisol</li> <li>Late night salivary cortisol</li> <li>Plasma ACTH</li> <li>Clinical signs of hypercortisolism</li> <li>Health-related Quality of Life</li> </ul>
<b>Safety assessments</b>	<ul style="list-style-type: none"> <li>Physical examination</li> <li>Vital signs</li> <li>Karnofsky performance status</li> <li>Laboratory evaluations (hematology, clinical chemistry, liver function testing, coagulation, urinalysis)</li> <li>Pregnancy and assessments of fertility</li> <li>Gallbladder ultrasound</li> <li>Cardiac assessments</li> <li>Echocardiogram</li> </ul>

<b>Data analysis</b>	<p>The proportion of patients with normalized mUFC at week 35 will be reported along with its corresponding asymptotic 95% CI.</p> <p>The primary endpoint: Proportion of patients who attain mUFC <math>\leq 1.0</math> ULN at week 35 with pasireotide alone or in combination with cabergoline</p> <p>The main secondary endpoints are:</p> <ol style="list-style-type: none"><li>1. Actual and percentage change in mUFC from baseline to study end at each scheduled visit when UFC is measured</li><li>2. Proportion of patients that attain mUFC <math>\leq 1.0 \times</math> ULN as assessed at each scheduled visit when UFC is measured</li><li>3. Proportion of patients who attain mUFC <math>\leq 1.0 \times</math> ULN or have at least 50% reduction from baseline in mUFC as assessed at each scheduled visit when UFC is measured</li></ol>
<b>Key words</b>	Cushing's disease, pasireotide, cabergoline, mUFC, ACTH-dependent, pituitary adenoma

## 1 Background

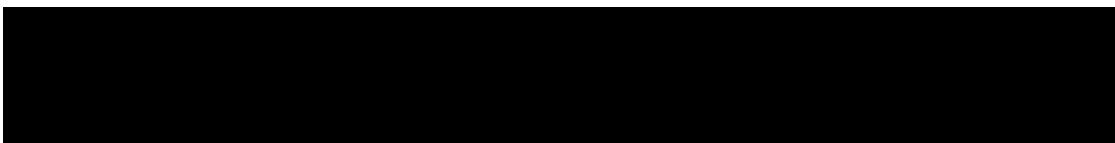
### 1.1 Overview of disease pathogenesis, epidemiology and current treatment

Cushing's disease (CD) is a rare but debilitating disease. Patients have excessive adrenocorticotrophic hormone (ACTH) secretion from a benign pituitary adenoma, which stimulates the adrenal glands to produce excess cortisol. The incidence of Cushing's disease ranges from 1-3 patients per million per year. Cushing's disease is associated with severe morbidity and premature mortality and most commonly affects adults aged 20-50 years of age, primary females. Patients suffer from this disease for many years before coming to medical attention and appropriate diagnosis.

The most common pathological finding in these patients is bilateral hyperplasia of the adrenal cortex and cortisol hypersecretion due to excessive ACTH secretion. The primary clinical signs and symptoms of Cushing's disease are due to hypercortisolism and include: changes in body habitus (moon facies, increased supraclavicular fat pad and dorsocervical hump), hirsutism, skin changes (easy bruising, purplish striae, reddening of the cheeks), generalized weakness and fatigue, wasting of musculature (particularly proximal muscles), menstrual disorders, decreased fertility and/or libido, hypertension, weight gain, decreased insulin sensitivity with disorders in glucose metabolism (including impaired glucose tolerance and diabetes mellitus), dyslipidemias (including elevated levels of triglycerides and low HDL cholesterol), mental disorders ranging from mood and behavior disorders, to depression and psychosis, sleep disturbances, osteopenia/osteoporosis, and immunosuppression with increased risk for infections. Because of these alterations patients with Cushing's disease have increased morbidity and mortality. Most patients also develop a high set-point for feedback inhibition of ACTH secretion by cortisol. Thus some patients may present with hypercortisolemia, with ACTH levels within normal limits.

Hypercortisolism is also known as Cushing's syndrome. Cushing's disease is one form of Cushing's syndrome. There are other disorders that lead to endogenous hypercortisolism. These include the ectopic production of ACTH by a tumor outside the pituitary gland and excessive secretion of cortisol by an adrenal tumor or adrenal hyperplasia.

The diagnosis of Cushing's disease requires a multi-step approach. In a patient who presents with the medical history and physical examination suggestive of hypercortisolism the first step is to confirm the presence of pathologic endogenous hypercortisolism. Several laboratory tests and diagnostic techniques are available for the diagnosis of Cushing's syndrome and these include: 24-hour urine free cortisol (UFC) measurements, blood sampling for serum cortisol levels, late-night salivary cortisol measurements, the low-dose dexamethasone suppression test (LDDST) and a combination of a LDDST with corticotrophin-releasing hormone (CRH) stimulation (Arnaldi 1995). The next step is to determine if the hypercortisolism is independent (adrenal Cushing's syndrome) or ACTH dependent (CD or ectopic ACTH). If the plasma ACTH level is below the lower limit of normal (suppressed) the patient has an ACTH-independent Cushing's syndrome. If the plasma ACTH level is normal or elevated the patient has ACTH-independent Cushing's syndrome. The third step is to



distinguish Cushing's disease from ectopic ACTH. Thus, a confirmation of a pituitary source of ACTH secretion is needed. This includes evidence of pituitary tumor > 6mm on MRI scan or confirmation by bilateral inferior petrosal sinus sampling (BIPSS) after corticotrophin-releasing hormone (CRH) stimulation test. In the BIPSS, if the petrosal to peripheral ratio of adrenocorticotrophin concentration is greater than or equal to 3.0 after CRH stimulation, a diagnosis of Cushing's disease can be made ([Arnaldi 1995](#)).

While surgical removal of the adenoma is first line therapy for CD, the success rate of surgery is between 65-90% for microadenomas (tumours < 1 cm) with recurrence rates between 10 to 20% after 10 years. The surgical cure rate for macroadenomas (>1 cm) is less than 65% and recurrence rates as high as 45% ([Biller 2008](#)). Surgery is in many cases complicated by hypopituitarism, which requires complicated life-long hormonal replacement therapies necessary to sustain life.

Irradiation of the pituitary is another treatment option but it may take many years to be effective and it is curative in only 15 to 45% of the cases. In addition, due to its lack of specificity the procedure very often results in hypopituitarism. Furthermore, there is a 1 to 2% risk of development of secondary tumours in the field of radiation over subsequent years ([Biller 2008](#)).

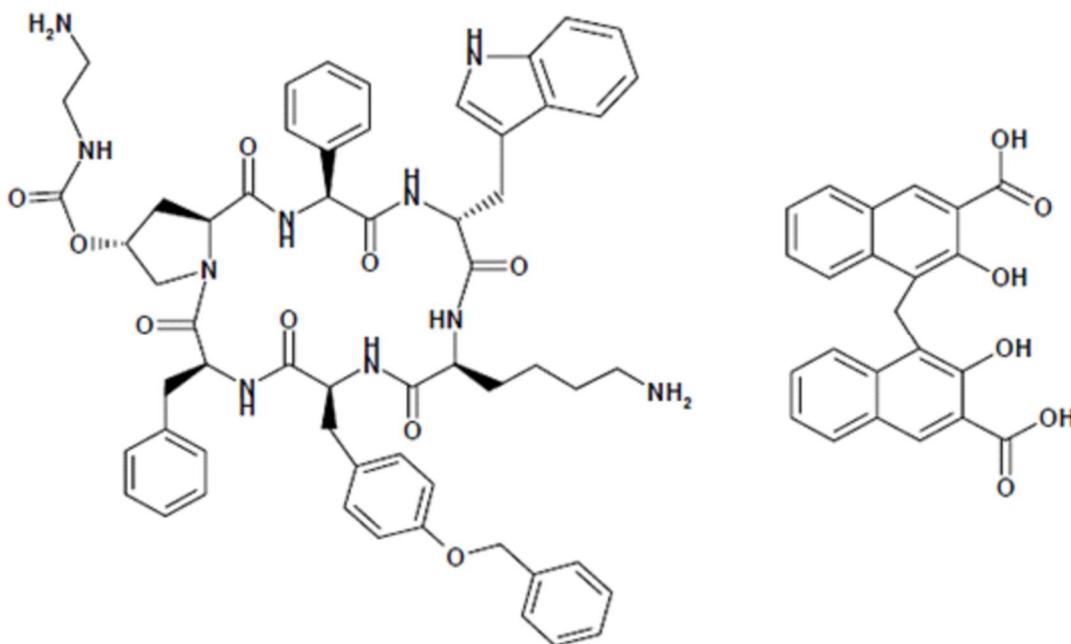
When surgery and/or irradiation fail, or for those patients for whom such therapies are not an option, the remaining alternatives are pharmacological treatment or bilateral adrenalectomy. Therefore, for patients who have failed surgery - either with persistent hypercortisolism soon after surgery or with recurrent hypercortisolism months or years after surgery - medical therapy is an option. A safe and effective targeted medical therapy is highly desirable in this patient population. There is an unmet medical need for the treatment of CD as medical treatment options are limited.

## **1.2 Introduction to investigational treatment(s) and other study treatment(s)**

### **1.2.1 Overview of Pasireotide**

Pasireotide is the first pituitary-targeted medical treatment approved for patients with Cushing's disease. It is an injectable somatostatin analogue. It is a novel cyclohexapeptide containing the structural elements [[[2-aminoethyl)amino]carbonyl]oxy]-L-proline, phenylglycine and tyrosine (benzyl), with the following structural and molecular formula ([Figure 1-1](#)):



**Figure 1-1** Pasireotide structural and molecular formula

Pasireotide free base on anhydrous basis: C<sub>58</sub>H<sub>66</sub>N<sub>10</sub>O<sub>9</sub>

Di-aspartate salt form on anhydrous basis: C<sub>58</sub>H<sub>66</sub>N<sub>10</sub>O<sub>9</sub> • 2 C<sub>4</sub>H<sub>7</sub>NO<sub>4</sub>

Like natural somatostatin and other somatostatin analogues (SRIFa), pasireotide exerts its pharmacological activity via binding to somatostatin receptors (sst). There are five known somatostatin receptors: sst 1, 2, 3, 4 and 5. Somatostatin receptors are expressed in different tissues under normal physiological conditions. Somatostatin analogues activate these receptors with different potencies and this activation results in a reduced cellular activity and inhibition of hormone secretion. Somatostatin receptors are strongly expressed in many solid tumors, especially in neuroendocrine and pituitary tumors where hormones are excessively secreted e.g. acromegaly ([Freda 2002](#)), GEP/NET tumors ([Oberg 2004](#)) and Cushing's disease ([van der Hoek 2005a](#)).

The SRIFa currently approved for use in the clinic (octreotide and lanreotide) have a high affinity to the sst subtype 2 (sst2), with moderate or no affinity to the remaining subtypes. While these SRIFa are effective for the pharmacological management of acromegaly and GEP/NET tumors patients, clinical studies with Cushing's disease have been unsuccessful ([Lamberts 1989](#), [Stalla 1994](#)).

In vitro studies have shown that corticotroph tumor cells from Cushing's patients display a strong expression of sst5 whereas the other receptor subtypes are either not expressed or are expressed at a significantly lower level. In addition, sst2 receptors but not sst5 receptors on corticotroph cells are down-regulated in the presence of glucocorticoids ([Hofland 2005](#), [van der Hoek 2005b](#)). Cushing's disease patients have high levels of circulating cortisol, which probably leads to a reduced expression of sst2 receptors. This observation could explain why currently available SRIF analogues have been largely unsuccessful in the treatment of these patients.

In contrast to other SRIFs, pasireotide has a high affinity to four of the five known sst subtypes (sst1, 2, 3 and 5) resulting in a unique binding profile, the closest to-date to the natural somatostatin. The broader binding profile of pasireotide, especially its high affinity to sst5, suggests it may be effective for the treatment of Cushing's disease patients. Several functional pre-clinical data derived from rats (Silva 2005), AtT20 cells and human corticotroph adenoma cells strongly support this assumption (Hofland 2005, van der Hoek 2005a). Additionally, clinical data from the POC study [CSOM230B2208] show that pasireotide has activity in Cushing's disease patients. In this study, pasireotide produced a decrease in UFC levels in 76 % of patients with Cushing's disease during the treatment period of 15 days. Serum cortisol levels and plasma ACTH levels were also reduced.

### **1.2.1.1 Non-clinical experience**

Preclinical data on binding affinity and functional activity in vitro and efficacy on hormone secretion in vivo have been obtained with the s.c. formulation in rats, dogs, mice and monkeys. Long-term in vivo studies performed using drug application by osmotic mini-pumps (Bruns 2002, Weckbecker 2002) have shown not only that the inhibitory effect of pasireotide was stronger, but also that there was less response escape (Bruns 2002). Osmotic mini-pumps release a drug substance in a constant, predefined way and thus mimic the constant release pattern of a LAR formulation. Based on the known efficacy of pasireotide on hormone secretion after long-term application, no additional pharmacological experiments with the new LAR formulation are considered necessary.

A detailed summary of available preclinical data is provided in the [Investigator's Brochure].

### **1.2.1.2 Clinical experience**

The pasireotide s.c. formulation has been evaluated in 7 studies with healthy volunteers, 1 study in patients with hepatic dysfunction, 2 studies with acromegalic patients, 1 study in patients with metastatic carcinoid tumors, and 2 studies in patients with Cushing's disease. A detailed summary of the clinical data is provided in the [Investigator's Brochure].

Single doses of pasireotide s.c. up to 1.5mg q.d. and 0.75mg b.i.d. multiple s.c. doses (7-14 days) up to 1.5mg q.d., 0.75mg b.i.d. and 2.1mg b.i.d. (up to 5 days), and continuous (7- day) s.c. infusion by insulin pump, have been well-tolerated, with mostly mild, transient side effects reported. The most commonly reported adverse events (AEs) were GI related as mild diarrhea and nausea requiring no treatment or study discontinuation. The frequency of these AEs appeared to decrease with time in multiple-dose studies.

An effect of pasireotide on QTcF interval at supra-therapeutic doses of 1.95mg s.c. b.i.d was observed in healthy volunteers [CSOM230B2113]. The placebo subtracted QTcF change from baseline showed a peak effect at 2-hours post-dose of pasireotide s.c. of 17.5 ms. In vitro electrophysiology data from the hERG channel assay revealed no inhibition of the hERG tail currents up to 10  $\mu$ M (10472 ng/mL) and pasireotide did not exert any electrophysiological effects on rabbit Purkinje fibers up to the concentration of 30  $\mu$ M (31416ng/mL). Further, no interference with any of the major ion cardiac channels [potassium (KCNQ1 and Kv3.4/Kir3.1) sodium (Nav1.5) and calcium (Cav1.2)] was seen at concentrations up to 30  $\mu$ M (31.42  $\mu$ g/ml). A single dose telemetry study in male monkeys, after subcutaneous

administration, was performed with doses of up to 2 mg/kg, with no effect on cardiovascular function.

Analysis of the clinical database does not indicate that the QT prolonging effect of pasireotide translates into an increased risk of arrhythmias (there were no reports of torsades de pointes during clinical experience with pasireotide and the incidence of notable QTc outliers of interest (new QTcF >480 ms, QTcF > 500ms, and QTcF change from baseline > 60 ms) in the overall pasireotide-exposed population was low, ranging from 0.3% to 1.9%. The incidence of AEs indicative of arrhythmogenic potential was low, and most cases were confounded by comorbidities. There was a single 'Electrocardiogram QT prolonged' SAE leading to study drug discontinuation (B2305-0771/00003). There was no evidence that the occurrence of AEs indicative of arrhythmogenic potential was related to the occurrence of cardiac arrhythmia.

A phase I study [[CSOM230B2124](#)] evaluating the effects of 4 classes of antihyperglycemic agents along with pasireotide for 7 days evaluated the glucose metabolism effects in healthy volunteers. Plasma glucose AUC0-4hr values during oral glucose tolerance test were increased from baseline by 69% after pasireotide alone, whereas lower increases of 60%, 49%, 38% and 19% were observed after co-administration of metformin, nateglinide, vildagliptin and liraglutide, respectively. Overall, the combination of pasireotide and anti-hyperglycemic agents was safe. The most frequent AEs were injection site reaction and GI related (diarrhea and nausea).

Data from the proof-of-concept Study [[CSOM230B2208](#)] in patients with Cushing's disease showed a reduction in mean urinary free cortisol levels (mUFC). Of the 39 patients enrolled on 0.6mg s.c. b.i.d of pasireotide, 29 qualified for the efficacy analysis of mUFC. During the initial 15 day treatment period (core study), five of the 29 evaluable patients (17.2%) achieved normalization of mUFC, the primary endpoint of this study. Twenty-two patients (75.9%) experienced reductions in the mUFC levels by Day 15. Of the 39 patients that received pasireotide the most frequent adverse events were diarrhea (51.3%), hyperglycemia (35.9%) and nausea (30.8%).

Subsequently a Phase III Study [[CSOM230B2305](#)] evaluated the efficacy and safety of two doses of pasireotide s.c. (0.6 and 0.9 mg s.c. b.i.d.) in 162 patients with mostly moderate to severe CD by evaluating the normalization of mUFC values at six months of treatment. A 0.3mg s.c. b.i.d. dose of pasireotide was evaluated as a lower dose and was effective for a small number of patients. The study confirmed that pasireotide is effective in the treatment of hypercortisolism in CD. At Month 6, 21 of 80 patients (26.3%; 95% CI 16.6%, 35.9%) randomized to pasireotide 0.9mg b.i.d. were considered to be responders (i.e. mUFC  $\leq$  ULN, with no dose increase). In the 0.6mg b.i.d. dose group, 12 of 82 patients (14.6%; 95% CI 7.0%, 22.3%) responded. The mUFC decreased in both treatment groups. The mean absolute changes from baseline in mUFC were -463.4 and -363.9 nmol/24h respectively for 0.6mg b.i.d. and 0.9mg b.i.d. Both doses had similar median percent reductions from Baseline to Month 6 in mUFC (approximately 48% for both doses). Robust reductions in mUFC occurred relatively quickly, within the first month, and were sustained over the course of Months 6 and 12 [[CSOM230B2305](#)]. Both doses were efficacious in lowering mUFC with the mean mUFC values and the median % changes in mUFC from baseline being similar between doses. See [Figure 1-2](#) below:

**Figure 1-2 Mean (+/- SE) urinary free cortisol (nmol/24h) at time points up to Month 12 by randomized dose group (Full analysis set - study B2305)**

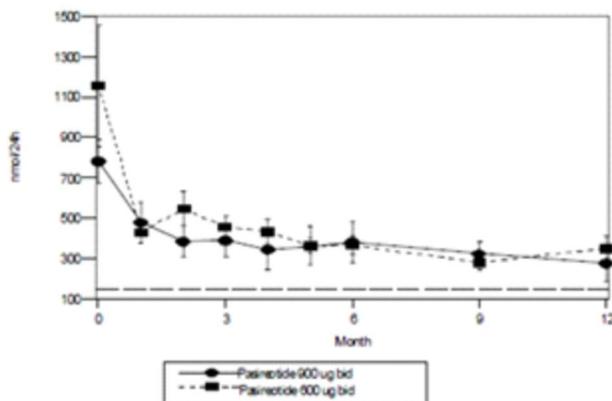


Figure 1-2: At least three 24h UFC assays contributed to patient mean results at Months 0 (baseline), 3, 6 and 12. At least two 24h UFC assays contributed to patient mean results at other time points.

+/-Standard errors are displayed.

— — — is the ULN for the UFC assay (145 nmol/L)

Overall, as mUFC decreased, continuous measures of the signs of Cushing's disease (e.g. blood pressure, weight and serum lipid levels) tended to improve. Both groups demonstrated increases in health-related quality of life (HRQL) scores at Months 6 and 12. The mean percent changes from baseline in HRQL scores at Month 6 were 31.3% and 73.0%, respectively, for the 0.6 and 0.9mg b.i.d. groups. The mean percent changes from baseline in HRQL scores at Month 12 showed an additional increase with 38.9% and 91.8%, respectively, for the 0.6 and 0.9mg b.i.d. groups.

Patients who had a baseline mUFC between 1.5 to 5 x ULN showed a greater response rate than patients with a baseline mUFC > 5x ULN (27.2% vs. 8.2%, respectively). Uncontrolled patients (those who did not normalize UFC and had less than 50% reduction from baseline in UFC) could be identified early in the treatment course with a high degree of certainty. Approximately 90% of patients with uncontrolled mUFC at both Months 1 and 2 were also uncontrolled at Months 6 and 12.

Pasireotide was well-tolerated. The majority of AEs were consistent with the known adverse drug reactions of Somatostatin Analogs (SSAs). The most common AEs (incidence  $\geq 10\%$ ) were diarrhea, nausea, abdominal pain, cholelithiasis, hyperglycemia, diabetes mellitus, fatigue and glycosylated hemoglobin increased. Hyperglycemia-related AEs appeared to be the most significant safety concern in terms of frequency of occurrence as well as overall clinical impact (i.e. overall increase in HbA1c of  $\sim 1.5\%$  for both dose groups at 6 and 12 months). Hyperglycemia was managed with the addition or adjustment in oral antidiabetic treatment or in some cases the addition of insulin. Patients who had pre-existing diabetes had a higher degree of hyperglycemia. As expected in successful therapies for hypercortisolism, AEs related to cortisol withdrawal (hypocortisolism) were reported in 13 (8.0%) patients, for which a dose decrease resulted in effective management of the AE.

Overall, pasireotide demonstrated a favorable benefit/risk profile in Cushing's disease. Importantly, patients that are relatively poor responders to pasireotide can be identified early

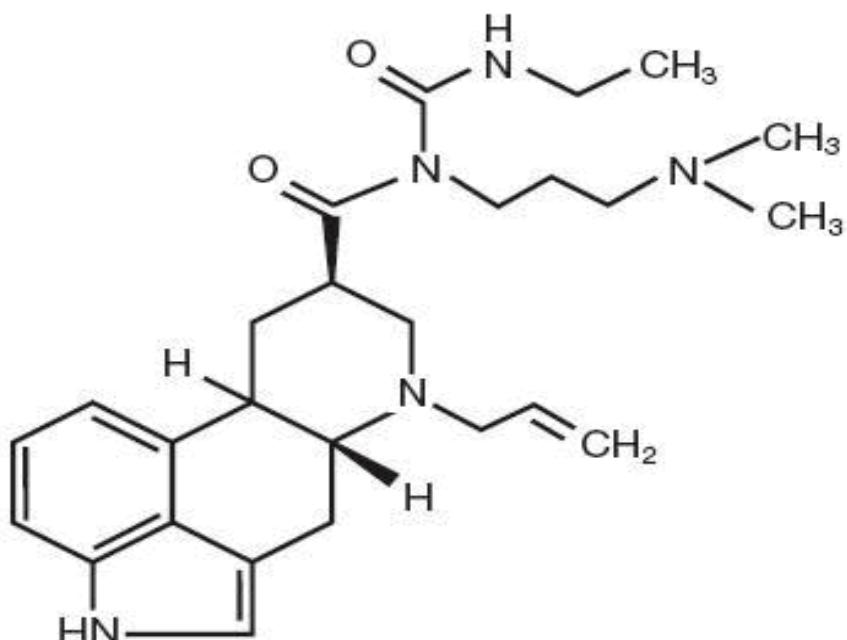
(i.e. after two months of treatment) with a high degree of certainty, thereby giving the option of prompt discontinuation of patients not likely to derive benefit from this drug.

Preliminary data (Feelders 2010) indicate synergic effect between pasireotide and cabergoline in increasing the biochemical control rate in patients with CD. When cabergoline was added to pasireotide in a proof of concept study, UFC normalization increased from 29% to 53%. These preliminary data make cabergoline the best partner for pasireotide in increasing biochemical control rate.

### 1.2.2 Overview of Cabergoline

Cabergoline USP is a dopamine receptor agonist. The chemical name for Cabergoline is 1-[(6-allylergolin-8 $\beta$ -yl)-carbonyl]-1-[3-(dimethylamino)propyl]-3-ethylurea and has the following structural formula (Figure 1-3):

**Figure 1-3** Cabergoline structure and molecular formula



$C_{26}H_{37}N_5O_2$  M. W. 451.62

#### 1.2.2.1 Non-clinical experience

The secretion of prolactin by the anterior pituitary is mainly under hypothalamic inhibitory control, likely exerted through release of dopamine by tuberoinfundibular neurons. Cabergoline is a long-acting dopamine receptor agonist with a high affinity for D2 receptors. Results of in vitro studies demonstrate that Cabergoline exerts a direct inhibitory effect on the secretion of prolactin by rat pituitary lactotrophs. Cabergoline decreased serum prolactin levels in reserpinized rats. Receptor-binding studies indicate that Cabergoline has low affinity for dopamine D1,  $\alpha$ 1- and  $\alpha$ 2- adrenergic, and 5-HT1- and 5-HT2-serotonin receptors.

Like somatostatin receptors, dopamine receptors (DRs) are also expressed in most cell types of the anterior pituitary gland. The DR family consists of 5 receptor subtypes that, on the basis of functional and pharmacological properties, can be subdivided into D1-like (D1 and D4) and D2-like (D2, D3, and D4) receptors. D1-like receptors are preferentially stimulatory, whereas D2-like receptors have mainly inhibitory properties (Missale 1998) D2 and, to a lesser extent, D4 are the DR subtypes that are expressed in the anterior pituitary gland. The most well-known action of DR in the regulation of anterior pituitary hormone secretion is the inhibition of prolactin secretion. Corticotroph adenomas express predominantly D2 receptors, as demonstrated by *in situ* hybridization studies, RT-PCR, and immunohistochemistry (Pivonello 2004). In Stefanescu L et al, The expression of D2 in corticotroph adenomas is positively correlated to the suppressive effects of cabergoline on urinary free cortisol (UFC) secretion in patients with CD (Pivonello 2004). Unlike sst2, but resembling sst5, D2 appears not to be negatively regulated by cortisol (de Bruin 2009).

### **1.2.2.2 Clinical experience**

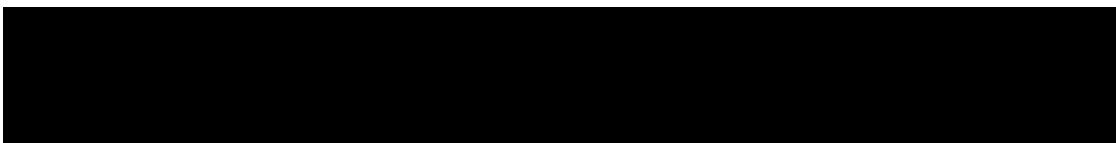
Early studies already showed that short-term treatment with the dopamine agonist bromocriptine inhibits ACTH and cortisol levels in 40% of patients with CD, Lamberts SW et al., although data on the efficacy of bromocriptine in patients with Cushing's disease appeared equivocal (Miller JW 1993). More recently, Pivonello et al (Pivonello 2004) showed that a 3-month treatment with cabergoline induced normalization of UFC in 40% of a series of 20 patients with recurrent or persistent Cushing's disease. In another study by Godbout et al (Godbout 2010), it was shown that cabergoline monotherapy was able to normalize UFC in 11 of 20 patients (37%) after short-term treatment with cabergoline and in 30% of patients with CD after long-term cabergoline treatment (at least 2 y, and in some for 5 y; mean dose, 2.1 mg/wk). However, during the long-term treatment with cabergoline monotherapy, a significant number of patients showed a treatment-escape to cabergoline treatment. This effect was shown even after several years of treatment in Pivonello R et al. (Pivonello 2004) and Godbout A et al (Godbout 2010).

## **2 Rationale**

### **2.1 Study rationale and purpose**

The treatment of patients with CD requires a multimodality approach. One approach is represented by medical treatment. Pasireotide, the first pituitary-targeted medical therapy approved for patients with CD showed efficacy in a proportion of patients in the registration study [SOM230B2305]. Overall results from the pivotal study demonstrated that pasireotide has a favorable benefit/risk profile in Cushing's disease. However, it was noted that some 65% and 48% of the patients completed 6- and 12-month treatment, respectively. Apart from the very beginning of the study, the main reason for discontinuation was due to insufficient therapeutic effect.

Cabergoline is often used in this indication in order to decrease cortisol levels; the literature has shown evidence of short-term efficacy but the long-term treatment highlighted treatment escapes in many patients. Therefore, combining medical treatment modalities can be considered in order to improve patient outcome.



Taking into consideration that biochemical remission should be rapidly achieved to reverse morbidity and mortality, drugs can be combined to control cortisol production within an acceptable time frame. If biochemical remission has been accomplished, drug dosage may be decreased or one of the used drugs may be withdrawn. Second, combining drugs may allow for lower doses with concomitantly less adverse events. Third, combining drugs may have potentiating effects on ACTH secretion by corticotroph tumor cells. Because most corticotroph adenomas simultaneously express sst5 and D2, it can be anticipated that a combination of sst5- and D2-targeting drugs may have additive or synergistic effects on ACTH secretion. In vitro data indeed indicate synergism between sst and D2 that might increase therapeutic efficacy.

Feeiders et al ([Feeiders 2010](#)) evaluated a medical stepwise approach in the management of 17 patients with Cushing's disease. The results of this study indicate synergic effect between pasireotide s.c. and cabergoline in increasing the biochemical control rate in patients with CD. Seventeen patients with Cushing's disease were started on pasireotide 0.1 mg tid for 2 weeks and the dose of pasireotide was increased to 0.25 mg tid should mUFC be elevated at the end of the 2-week period. After one month treatment, cabergoline at the dose 1.5 mg every other day was added to pasireotide in the patients who did not achieve biochemical control on pasireotide monotherapy. When cabergoline was added to pasireotide, UFC normalization increased from 29% to 53%. The improvement in cortisol secretion was accompanied by ameliorations in the classical features of Cushing's disease. The safety profile of the combination is consistent with the ones of the two single compounds. These preliminary data make cabergoline the best partner for pasireotide in increasing biochemical control rate.

The purpose of this prospective, multicenter, open-label phase II study, is to evaluate the efficacy and safety of pasireotide alone or in combination with cabergoline in patients with Cushing's disease as measured by the proportion of patients achieving normal UFC at the end of the study period. The study will enroll patients who are pasireotide-untreated at the time of screening and patients who are currently on treatment with maximal tolerated doses of pasireotide but still with uncontrolled mUFC.

## 2.2 Rationale for the study design

This is an open-label, multi-center international non-comparative study with adult patients with confirmed diagnosis of Cushing's disease. The study will consist of patients who have never received pasireotide or patients who have received pasireotide sometimes in the past but was discontinued for reasons not related to safety. The study will also enroll pasireotide-treated patients who at the time of screening have not achieved biochemical control despite maximal tolerated doses of pasireotide for at least 8 weeks.

Pasireotide naïve patients will start pasireotide monotherapy at the dose of 0.6 mg s.c. bid. If at the end of the 8 week treatment period, the biochemical control is not achieved and the 0.6mg bid dose is well tolerated, the pasireotide dose will be increased to 0.9mg bid. If the 0.9mg bid dose of pasireotide does not lead to biochemical control, cabergoline will be added with a starting dose of 0.5mg qd. If the combination dose of 0.9mg bid of pasireotide plus 0.5mg qd cabergoline does not achieve biochemical control, the cabergoline dose will be increased to 1.0mg qd.



Patients who are currently treated with maximal tolerated doses of pasireotide monotherapy for at least 8 weeks at screening without achieving normal mUFC will enter the study with combination therapy with cabergoline. Cabergoline starting dose will be 0.5mg qd.

The stepwise approach implemented in the trial is consistent with clinical practice where patients are first started on monotherapy and, if necessary, combinations are considered.

### **2.3 Rationale for dose and regimen selection**

Pasireotide naïve patients or patients who have received pasireotide sometime in the past but was discontinued for reasons not related to safety, will start pasireotide dose of 0.6 mg bid with the possibility of increase to 0.9 mg bid. In case of safety issues, the dose of the medication can be decreased from 0.6 mg bid to 0.3 mg bid or from 0.9 mg bid to 0.6 mg bid, respectively. The doses used in the study are the ones currently approved by Health Authorities.

Patients currently treated with pasireotide at 0.3mg bid, 0.6mg bid or 0.9mg bid, whichever the maximal tolerated dose they have reached, will start with combination treatment of pasireotide plus 0.5mg of cabergoline qd. The dose of cabergoline is consistent with the one used in the studies published by Pivonello ([Pivonello 2004](#)) and by Feelders ([Feelders 2010](#)). The daily schedule selected in the trial has the objective to increase patient's compliance with the treatment. Furthermore, when higher doses of cabergoline are required, such as in acromegaly, a daily schedule is always chosen. Higher doses than the one used in the current trial are not expected to provide further benefit.



### 3 Objectives and endpoints

**Table 3-1 Objectives and related endpoints**

Objective	Endpoint	Analysis
<b>Primary</b>		Refer to <a href="#">Section 10.2.2</a>
1. To evaluate the overall efficacy of the treatment regimen of pasireotide alone or in combination with cabergoline in patients with Cushing's disease	1. Proportion of patients who attain mUFC $\leq 1.0 \times \text{ULN}$ at week 35 with pasireotide alone or in combination with cabergoline	
<b>Secondary</b>		Refer to <a href="#">Section 10.3</a>
1. To assess the changes in mUFC from baseline to study end at each scheduled visit where UFC is measured	1. Actual and percentage change in mUFC from baseline to study end at each scheduled visit when UFC is measured	
2. To assess overall efficacy of pasireotide alone or in combination with cabergoline as measured by normal mUFC levels at each scheduled visit when UFC is measured	2. Proportion of patients that attain mUFC $\leq 1.0 \times \text{ULN}$ as assessed at each scheduled visit when UFC is measured	
3. To evaluate overall efficacy of pasireotide alone or in combination with cabergoline as measured by controlled and partially controlled mUFC levels at each scheduled visit when UFC is measured	3. Proportion of patients who attain mUFC $\leq 1.0 \times \text{ULN}$ or have at least 50% reduction from baseline in mUFC as assessed at each scheduled visit when UFC is measured	
4. To evaluate the duration of controlled or partially controlled mUFC response	4. Duration of controlled or partially controlled response is defined as the period starting from the date of patient's first normalization (mUFC $\leq 1.0 \times \text{ULN}$ ) or at least 50% reduction from baseline up to the date when the patient's mUFC $> 1.0 \times \text{ULN}$ and the reduction from baseline falls to less than 50% from the first time	
5. To assess the effect on plasma ACTH and serum cortisol	5. Change from baseline in plasma ACTH and serum cortisol over time	
6. To assess the effect on the continuous measures of clinical symptoms of hypercortisolism	6. Actual and percentage change from baseline in clinical symptoms over time: blood pressure, body mass index, waist circumference, fasting serum lipid profile, and weight	
7. To assess the effect on the categorical measures of clinical signs of hypercortisolism	7. Shift from baseline in clinical signs over time: facial rubor, fat pads, hirsutism, striae (via photographs) and muscle strength	

Objective	Endpoint	Analysis
8. To assess the improvement of health-related quality of life	8. Change from baseline in standardized scores, as measured by the Cushing's QOL and SF-12v2 over time	
9. To evaluate the safety profile of pasireotide alone or in combination with cabergoline	9. Toxicity will be assessed using the National Cancer Institute-Common Toxicology Criteria Adverse Events version 4.03 (NCI-CTCAE v4.03) and for laboratory assessments that include biochemistry, hematology, urinalysis; special safety assessments that include the regular monitoring and recording of blood glucose, insulin, HbA1c, GH and IGF-1, thyroid and liver function tests, gallbladder examinations and ECGs. Concomitant medications/Significant nondrug therapies will be assessed from study enrollment until the safety follow-up visit.	
Other secondary	Not applicable	

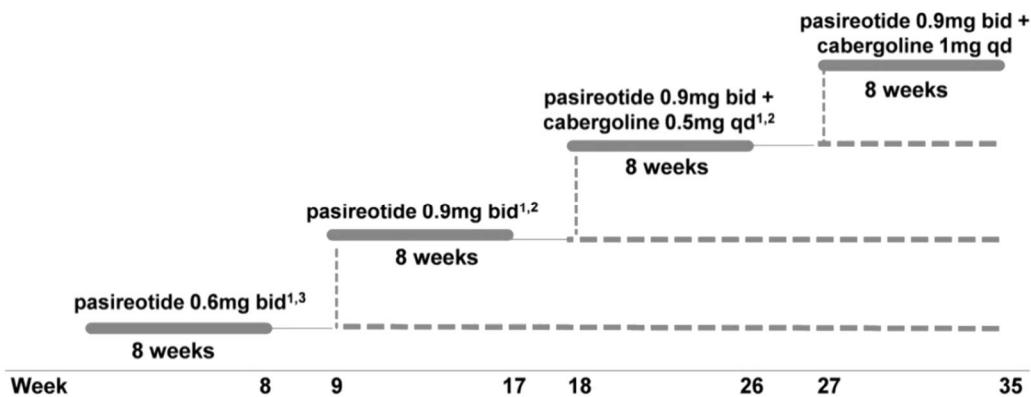
## 4 Study design

### 4.1 Description of study design

#### Core Phase

Pasireotide-untreated patients at screening - this includes patients who have never received pasireotide or patients who have received pasireotide sometime in the past but it was not discontinued because of safety - will start on pasireotide at 0.6mg twice a day for 8 weeks. Should biochemical control not be achieved by week 8 and the tolerability of the 0.6mg dose is good, the dose of pasireotide will be increased to 0.9mg twice a day for another 8 weeks. If biochemical control is not achieved with the higher dose of pasireotide, cabergoline at increasing doses will be added, starting at 0.5mg once a day, and then increased to 1.0mg once a day. Dose adjustments for cabergoline due to safety issues are allowed. Patients will be treated for a total of 35 weeks, including three 1-week (+ 3 days) dose titration periods at weeks 8, 17 and 26. For details on dose titration, please refer to Dose Modification and Titration Guidelines section. Stepwise treatment schema is outlined in [Figure 4-1](#) Pasireotide-untreated patients at screening below:

**Figure 4-1** Pasireotide-untreated patients at screening

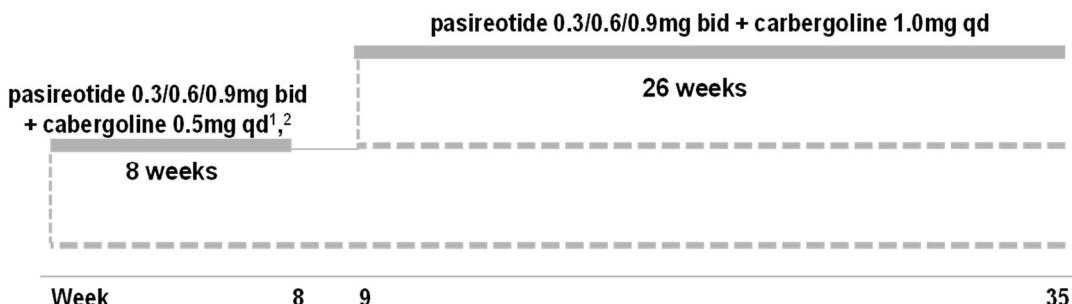


1. Patients not achieving normal UFC at the end of each treatment period will have the dose of the medication up-titrated to the next level
2. Patients must receive at least 8-week study treatment at each dose level in order to be titrated up to the next dose level, if biochemical control is not achieved
3. Patients that cannot have the dose up-titrated to 0.9mg because of safety reasons e.g. increased blood glucose levels will be treated with the combination pasireotide 0.6 mg and cabergoline at increasing doses. Patients who cannot tolerate 0.6mg bid will have the dose down-titrated to 0.3mg bid

Patients currently treated with maximal tolerated doses of pasireotide monotherapy for at least 8 weeks - 0.3mg twice a day, 0.6mg twice a day or 0.9mg twice a day for at least 8 weeks - but still did not achieve biochemical control will add cabergoline 0.5mg once a day at study entry. They will continue the combination treatment for 8 weeks. Should biochemical control

not be achieved by week 8, the dose of cabergoline will be increased to 1mg once a day and patients will be monitored for another 8 weeks. Dose adjustments for cabergoline due to safety issues are allowed. These patients will also be treated for a total of 35 weeks including one 1-week (+ 3 days) dose titration period at week 8. For details on dose titration, please refer to Dose Modification and Titration Guidelines section. Stepwise treatment schema is outlined in [Figure 4-2](#). Patients currently treated with maximal tolerated doses of pasireotide monotherapy below:

**Figure 4-2 Patients currently treated with maximal tolerated doses of pasireotide monotherapy**



1. Patients not achieving normal UFC at the end of each treatment period will have the dose of the medication up-titrated to the next level
2. Patients must receive at least 8-week of pasireotide 0.3/0.6/0.9mg bid + cabergoline 0.5mg qd in order to be titrated up to the next dose level, if biochemical control is not achieved

The total duration of the core phase will be 43 weeks (4 weeks of screening period, 35 weeks of study treatment + study completion visit occurring within 4 weeks of last dose). All patients not continuing into the extension phase will have a study completion visit 28 days (+/- 2 days) after last dose is received in the core phase.

### **Extension phase**

After 35 weeks of treatment in core phase, patients have the option to continue study treatment if pasireotide is not yet approved for commercial use and/or reimbursed - if country reimbursement is applicable - in each respective country, or until 31<sup>st</sup> December 2019, or once an applicable roll over protocol becomes available, or whichever occurs first. Novartis will have a local transition plan in order to ensure that all trial patients will still have access to the study medication without any delay in their treatment. Patients who come off the extension phase are required to complete a study completion visit 28 days (+/- 2 days) after last dose is received in the extension phase.

## 5 Patient population

The study population will consist of patients with persistent or recurrent Cushing's disease or patients with de novo Cushing's disease that are not considered candidates for pituitary surgery (poor surgery candidates, surgically unapproachable tumor, patients with no visible pituitary tumor, patients who refuse surgery). A confirmed Cushing's disease diagnosis is required.

The study will enroll a total of 64 patients.

The study population consists of patients who have never received pasireotide or patients who have received pasireotide sometime in the past but it was not discontinued because of safety. These patients will start pasireotide monotherapy at 0.6mg bid. In addition, patients who are currently treated with maximal tolerated doses of pasireotide monotherapy for at least 8 weeks at screening but with elevated muFC will enter the study with combination treatment of pasireotide at 0.3mg bid, 0.6mg bid, or 0.9mg bid, whichever the maximal tolerated dose they have reached, plus 0.5mg of cabergoline qd.

### 5.1 Key inclusion criteria

1. Written informed consent obtained prior to any screening procedures.
2. Adult patients with confirmed diagnosis of ACTH-dependent Cushing's disease as evidenced by all of the following:
  - a. The mean of three 24-hour urine samples collected within 2 weeks  $> 1 \times \text{ULN}$  with 2 out of 3 samples  $> \text{ULN}$
  - b. Morning plasma ACTH within the normal or above normal range
  - c. Either MRI confirmation of pituitary adenoma  $> 6$  mm, or inferior petrosal sinus gradient  $> 3$  after CRH stimulation for those patients with a tumor less than or equal to 6 mm\*. For patients who have had prior pituitary surgery, histopathology confirming an ACTH staining adenoma
  - d. \*If IPSS had previously been performed without CRH (e.g. with DDAVP), then a central to peripheral pre-stimulation gradient  $> 2$  is required. If IPSS had not previously been performed, IPSS with CRH stimulation is required. If surgery has been performed and histopathology indicates an ACTH-secreting tumor, there is no need for IPSS even for patients with a tumor  $< 6$  mm. If surgery has not been performed and the tumor is  $< 6$  mm, IPSS is required to confirm the diagnosis using CRH, or DDAVP if CRH is not available.
3. Patients with de novo Cushing's disease can be included only if they are not considered candidates for pituitary surgery (e.g. poor surgical candidates, surgically unapproachable tumors, patients who refuse to have surgical treatment)
4. Male or female patients aged 18 years or greater
5. Karnofsky performance status  $\geq 60$  (i.e. requires occasional assistance, but is able to care for most of their personal needs)

6. Patients on medical treatment for Cushing's disease the following washout periods must be completed before screening assessments are performed
  - Inhibitors of steroidogenesis (ketoconazole, metyrapone): 1 week
  - Pituitary directed agents: Dopamine agonists (bromocriptine, cabergoline) and PPAR $\gamma$  agonists (rosiglitazone or pioglitazone): 4 weeks
  - Octreotide LAR, Lanreotide SR and Lanreotide autogel: 14 weeks
  - Octreotide (immediate release formulation): 1 week
  - Progesterone receptor antagonist (mifepristone): 4 weeks
7. Patients can be considered to enter the trial if they meet any one of the following criteria:
  - They are naïve to pasireotide
  - They have received pasireotide in the past and have been discontinued because of lack of efficacy (2 weeks of washout prior to screening for patients treated with pasireotide subcutaneously and 12 weeks of washout prior to screening for patients treated with pasireotide LAR)
  - Patients who are on maximal tolerated dose but have not achieved biochemical control
8. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, if they are using highly effective methods of contraception during dosing and for 30 days after stopping study medication. Highly effective contraception methods include:
  - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
  - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
  - Male sterilization (at least 6 months prior to screening). For female subjects on the study the vasectomized male partner should be the sole partner for that subject.
  - Combination of any two of the following (a+b or a+c, or b+c):
    - a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
    - b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
    - c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.
9. Male participants in the trial must agree to use a condom during intercourse, and not to father a child during the study and for the period of 30 days following stopping of the study treatment.

## 5.2 Exclusion criteria

Patients must not meet any of the following exclusion criteria at screening:

1. Patients with compression of the optic chiasm causing any visual field defect that requires surgical intervention
2. Diabetic patients with poor glycemic control as evidenced by HbA1c >8%
3. Patients with risk factors for torsade de pointes, i.e. patients with a baseline QTcF >450 ms in males, and > 460 ms in females. hypokalemia, hypomagnesaemia, uncontrolled hypothyroidism, family history of long QT syndrome, or concomitant medications known to prolong QT interval
4. Patients with clinically significant valvular disease
5. Patients with Cushing's syndrome due to ectopic ACTH secretion
6. Patients with hypercortisolism secondary to adrenal tumors or nodular (primary) bilateral adrenal hyperplasia
7. Patients who have a known inherited syndrome as the cause for hormone over-secretion (i.e. Carney Complex, McCune-Albright syndrome, MEN-1)
8. Patients who are hypothyroid and not on adequate replacement therapy
9. Patients with symptomatic cholelithiasis
10. Patients who have congestive heart failure (NYHA Class III or IV), unstable angina, sustained ventricular tachycardia, clinically significant bradycardia, advanced heart block, history of acute MI less than one year prior to study entry or clinically significant impairment in cardiovascular function
11. Patients with liver disease such as cirrhosis, chronic active hepatitis, or chronic persistent hepatitis, or patients with ALT/AST > 2 X ULN, serum bilirubin >2.0 X ULN
12. Patients with serum creatinine >2.0 X ULN
13. Patients with WBC <3 X 10<sup>9</sup>/L; Hb 90% < LLN; PLT <100 X 10<sup>9</sup>/L
14. Patients who have a history of alcohol or drug abuse in the 6 month period prior to receiving pasireotide
15. Patients who have participated in any clinical investigation with an investigational drug within 1 month prior to dosing
16. Patients with active malignant disease within the last five years (with the exception of basal cell carcinoma or carcinoma in situ of the cervix)
17. Patients with the presence of active or suspected acute or chronic uncontrolled infection
18. Patients with a history of non-compliance to medical regimens or who are considered potentially unreliable or will be unable to complete the entire study
19. Patients with presence of Hepatitis B surface antigen (HbsAg)
20. Patients with presence of Hepatitis C antibody test (anti-HCV)
21. Patients with severe hepatic impairment (Child Pugh C) and hypersensitivity to pasireotide or cabergoline
22. Patients with lung, pericardial, and retroperitoneal fibrosis; gastro-duodenal ulcer or digestive hemorrhage, galactose intolerance, Parkinson's disease, uncontrolled hypertension and Raynaud's syndrome.

23. Pregnant or nursing (lactating) women where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test ( $> 5$  mIU/mL).
24. Patients with end-stage renal failure and/or hemodialysis

## **6 Treatment**

### **6.1 Patient numbering, treatment assignment**

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject Number is a 9-digit number consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available to the investigator. Once assigned, the Subject No. must not be reused for any other subject and the Subject No. for that individual must not be changed, even if the patient is re-screened. If the patient fails to be assigned to treatment for any reason, the reason will be entered into the Screening Disposition page

### **6.2 Study treatment**

Patients who are not treated with pasireotide at the time of screening or have never been treated with pasireotide in the past will start pasireotide 0.6mg twice a day for 8 weeks. If biochemical control is not achieved by the end of 8 weeks, and the 0.6mg dose is well-tolerated, the dose of pasireotide will be increased to 0.9mg twice a day for another 8 weeks. If biochemical control is not achieved with the higher dose of pasireotide, cabergoline will be added and patients will begin combination treatment with cabergoline at the starting dose of 0.5mg qd for 8 weeks. If biochemical control is still not achieved at the end of the third 8-week treatment period, the dose of cabergoline will be further increased to cabergoline at 1.0mg qd for another 8 weeks.

Patients that cannot have the dose up-titrated to 0.9mg bid because of safety reasons, for example, significantly increased blood glucose levels, will be treated with combination pasireotide 0.6mg bid and cabergoline at increasing doses. Patients who cannot tolerate pasireotide 0.6mg bid will have the dose down-titrated to 0.3mg bid and begin combination treatment with cabergoline at increasing doses should pasireotide 0.3mg bid monotherapy not be able to lead to normal mUFC. If a patient shows high sensitivity to pasireotide 0.6 mg bid resulting in cortisol values  $<LLN$  and/or signs/symptoms consistent with the diagnosis of hypocortisolism, the dose of pasireotide can be decreased to 0.3 mg bid. Despite the dose reduction, some patients may still present with cortisol values  $<LLN$  and/or signs/symptoms consistent with hypocortisolism; in this case the dose of pasireotide can be further reduced to 0.3 mg qd in order to achieve and maintain normal cortisol levels. Please refer to Dose modifications and titration guidelines [Section 6.4](#) of the protocol for more details.



At weeks 8, 17 and 26, patients will continue to receive their current dose until their UFC results are available, at which time, a decision will be made on whether to maintain the current dose or titrate up to the next level.

Patients who are currently treated with maximal tolerated doses of pasireotide monotherapy at 0.3mg, 0.6mg or 0.9mg twice a day for at least 8 weeks, but still with elevated UFC will immediately start the combination treatment by adding cabergoline 0.5mg once a day to their current pasireotide dose at study entry. Patients will continue with the combination treatment for 8 weeks. If biochemical control is not achieved by the end of the 8 weeks, the dose of cabergoline will be increased to 1mg once a day. At week 8, patients will continue to receive their starting combination dose until their UFC results are available, at which time, a decision will be made on whether to maintain the current dose or titrate up to the next combination dose.

All patients will be treated for a total of 35 weeks in the core phase.

The possible monotherapy or combination treatment regimens are as follows:

1. Monotherapy: pasireotide 0.3mg twice a day
2. Monotherapy: pasireotide 0.6mg twice a day
3. Monotherapy: pasireotide 0.9mg twice a day
4. Combination: pasireotide 0.3mg twice a day + cabergoline 0.5mg once a day
5. Combination: pasireotide 0.3mg twice a day + cabergoline 1.0mg once a day
6. Combination: pasireotide 0.6mg twice a day + cabergoline 0.5mg once a day
7. Combination: pasireotide 0.6mg twice a day + cabergoline 1.0mg once a day
8. Combination: pasireotide 0.9mg twice a day + cabergoline 0.5mg once a day
9. Combination: pasireotide 0.9mg twice a day + cabergoline 1.0mg once a day
10. Monotherapy: pasireotide 0.3mg once a day\*

\* This dosage should only be applied if a patient shows high sensitivity to pasireotide 0.6 mg bid resulting in cortisol values <LLN and/or signs/symptoms consistent with the diagnosis of hypocortisolism, the dose of pasireotide can be decreased to 0.3 mg bid. Despite the dose reduction, some patients may still present with cortisol values <LLN and/or signs/symptoms consistent with hypocortisolism; in this case the dose of pasireotide can be further reduced to 0.3 mg qd in order to achieve and maintain normal cortisol levels.

### **6.2.1 Dosing regimen**

For dose and treatment schedule, please see Table 6-1 below.

**Table 6-1 Dose and treatment schedule**

<b>Study treatments</b>	<b>Pharmaceutical form and route of administration</b>	<b>Dose</b>	<b>Frequency and/or Regimen</b>
Pasireotide	Subcutaneous	0.3mg, 0.6mg, and 0.9mg	Twice a day
Cabergoline	Oral	0.5mg or 1.0mg	Once a day

## **6.2.2 Treatment duration**

### **Core phase**

All patients will receive a total of 35-week treatment.

### **Extension phase**

After up to 35 weeks of treatment, patients have the option to continue study treatment if pasireotide is not approved for commercial use and/or reimbursed in each respective country, if country reimbursement is applicable. Patients can continue with study treatment on extension phase until pasireotide is approved for commercial use and reimbursed in their respective country, or until 31<sup>st</sup> December, 2019, or once an applicable roll over protocol becomes available, or whichever occurs first.

## **6.3 Study drug**

### **6.3.1 Supply, preparation and storage**

### **6.3.2 Pasireotide**

Please refer to pasireotide Package Insert and Summary of Product Characteristics (SmPC) for preparation and storage. Pasireotide will be supplied by Novartis if it is not available in the respective country.

### **6.3.3 Cabergoline**

Cabergoline is in the form of 0.5mg tablet. Cabergoline should be taken in the evening after a full meal. Dostinex, a generic form of cabergoline, will be used in the trial. If Dostinex is not available in a participating country, a different type of generic form will be used. For storage conditions, please refer to cabergoline Package Insert and SmPC. Cabergoline will be supplied by Novartis.

### **6.3.4 Study drug compliance**

Patients must be able to self-administer the study drug, pasireotide (subcutaneous injections) and are to receive instruction from the site staff or investigator on the correct procedures. They should be advised to avoid multiple injections at, or near the same site. Ampoules will not be reused; a new ampoule should be used for each injection. Patients should be instructed to retain and return unused ampoules at their next scheduled visit.

Patients will self-administer pasireotide subcutaneously twice a day 12 hours apart. It is advised to take the study medication at the same time every day at around 10:00 in the morning and 10:00 in the evening.

For patients who are unable to tolerate the protocol specified dosing schedule, dose adjustments are permitted to keep the patient on study drug. Please refer to the Dose Modification and Titration Guidelines section.



The investigator should instruct the patient to take the study drug exactly as described. All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record Case Report Form (CRF).

Patient should phone the investigator if he/she experiences an adverse event and their next study visit is not yet due. If dose delay or modification is required due to the adverse event, the investigator should document in the medical record the telephone conversation regarding the dose delay or modification.

## **6.4 Guidelines for dose modifications and titrations**

### **6.4.1 Pasireotide and cabergoline dose modification steps**

**Pasireotide untreated patients:** will begin their treatment with pasireotide 0.6mg twice a day monotherapy for 8 weeks. If biochemical control is not achieved by the end of the 8-week period, and the 0.6mg dose is well tolerated, the dose of pasireotide will be increased to 0.9mg twice a day for another 8 weeks. If biochemical control is still not achieved at 0.9mg twice a day and the dose is well tolerated, the combination treatment of pasireotide 0.9mg twice a day plus cabergoline 0.5mg once a day will be given for another 8 weeks. If biochemical control is not yet achieved either during or at the end of the 8-week period, cabergoline dose will be increased to 1.0mg once a day.

If a patient shows high sensitivity to pasireotide 0.6mg bid resulting in cortisol values <LLN and/or signs/symptoms consistent with the diagnosis of hypocortisolism, the dose of pasireotide can be decreased to 0.3mg bid. Despite the dose reduction, some patients may still present with cortisol values <LLN and/or signs/symptoms consistent with hypocortisolism; in this case the dose of pasireotide can be further reduced to 0.3 mg qd in order to achieve and maintain normal cortisol levels.

If the 0.9mg twice a day dose is not tolerated and biochemical control is not achieved, patient will begin combination treatment of pasireotide at 0.6mg twice a day plus cabergoline at 0.5mg once a day for 8 weeks. If during or at the end of the 8-week period, the biochemical control is not achieved, the combination dose will be increased to pasireotide at 0.6mg twice a day plus cabergoline at 1.0mg once a day for 8 weeks. The patient will continue with the highest combination dose of 0.6mg pasireotide twice a day plus 1.0mg cabergoline once a day, or 0.9mg pasireotide twice a day plus 1.0mg of cabergoline once a day for 8 weeks. The total duration of treatment is 35 weeks. (see [Table 6-2](#))

If patient does not tolerate 0.6mg twice a day, the dose of pasireotide should be decreased to 0.3mg twice a day. If pasireotide 0.3mg twice a day does not lead to biochemical control after at least 8 weeks of treatment, combination with cabergoline as described above can be initiated (see [Table 6-2](#)).

If patient cannot increase from 0.6mg twice a day to 0.9mg twice a day due to safety, and is not yet biochemically controlled, combination with cabergoline 0.5mg qd can be initiated right away with pasireotide at 0.6mg twice a day (see [Table 6-2](#)).

If patient is being escalated to 0.9mg twice a day, but cannot tolerate the dose, dose should be reduced to 0.6mg twice a day. If the latter dose does not lead to biochemical control, combination with cabergoline as described above can be initiated (see [Table 6-2](#)).

If combination pasireotide and cabergoline 0.5mg once a day is not tolerated, the dose of cabergoline can be reduced to 0.5mg every other day. If 0.5mg every other day is not tolerated, and biochemical control is not achieved, patient should be considered for discontinuation if no clinical benefit is derived (see [Table 6-2](#)).

If combination pasireotide and cabergoline 1.0mg once a day is not tolerated, the dose of cabergoline can be reduced to 1.0mg every other day. If 1.0mg every other day is not tolerated, and biochemical control is not achieved, patient should be considered for discontinuation if no clinical benefit is derived (see [Table 6-2](#)).

The minimum treatment of any regimen is 8 weeks. Patients losing biochemical control at any time point after the 8 week period will have the dose of the study medication increased immediately to the next level provided that the dose is well tolerated.

For patients whose starting dose is 0.6mg pasireotide twice a day monotherapy, at weeks 9, 18 and 27, before patient's UFC results are available, the investigator may select one of the following two options to dispense study medication to the patient for the next 5-9 weeks of treatment:

Option 1: The investigator dispenses study medication at the current dose, plus study medication at the next dose level at the end of week 8, 13, 17, 22, 26, or 31 visits. When patient's UFC results are available, the investigator should phone the patient to inform him/her to either remain at the current dose or titrate up to the next monotherapy dose level or start the combination therapy.

Option 2: The investigator dispenses study medication at the current dose at the end of week 8, 13, 17, 22, 26 or 31 visits. When patient's UFC results are available and shown that his/her biochemical is not controlled, the investigator schedules a visit for patient to come to the clinic and pick up study medication at the next monotherapy dose level or start the combination therapy.

The dosing decision should be properly documented in the medical record and dose administration CRF page.

**Table 6-2 Pasireotide and cabergoline dose modification steps for pasireotide un-treated patients**

Pasireotide: pasi Cabergoline: cabe	Starting dose level	Dose modification level - 1	Dose modification level - 2	Dose modification level - 3	Dose medication level - 4
Modification # 1	0.6mg bid pasi <sup>a</sup>	0.3mg bid pasi <sup>b</sup>	0.3mg bid pasi + 0.5mg cabe qd <sup>b</sup>	0.3mg bid pasi + 1.0mg cabe qd	
Modification # 2	0.6mg bid pasi <sup>b</sup>	0.9mg bid pasi <sup>b</sup>	0.9mg bid pasi + 0.5mg qd cabe <sup>b</sup>	0.9mg bid pasi + 1.0mg qd cabe	
Modification # 3	0.6mg bid pasi <sup>b</sup>	0.9mg bid pasi <sup>a</sup>	0.6mg bid pasi <sup>b</sup>	0.6mg bid pasi + 0.5mg cabe qd <sup>b</sup>	0.6mg bid pasi + 1.0mg cabe qd
Modification # 4	0.6mg bid pasi <sup>c</sup>	0.6mg bid pasi + 0.5mg qd cabe <sup>b</sup>	0.6mg bid pasi + 1.0mg cabe qd		
Modification # 5	0.9mg bid pasi <sup>ab</sup>	0.6mg bid pasi + 0.5mg qd cabe <sup>b</sup>	0.6mg bid pasi + 1.0mg qd cabe		

Pasireotide: pasi Cabergoline: cabe	Starting dose level	Dose modification level - 1	Dose modification level - 2	Dose modification level - 3	Dose modification level - 4
Modification # 6	0.3, 0.6 or 0.9mg bid pasi + 0.5mg qd cabe <sup>a</sup>	0.3, 0.6 or 0.9mg bid pasi + 0.5mg every other day cabe <sup>ab</sup>	Discontinuation if no clinical benefit		
Modification # 7	0.3, 0.6 or 0.9mg bid pasi + 1.0mg qd cabe <sup>a</sup>	0.3, 0.6 or 0.9 mg bid pasi + 1.0mg every other day cabe <sup>ab</sup>	Discontinuation if no clinical benefit		

<sup>a</sup> Dose modification is initiated if the current dose is not tolerated

<sup>b</sup> Dose modification is initiated if biochemical control is not achieved

<sup>c</sup> Dose cannot be increased to the next level due to toxicity but biochemical control is not achieved

**Patients currently treated with maximal tolerated doses of pasireotide monotherapy:**

0.3mg bid, 0.6mg bid or 0.9mg bid, for at least 8 weeks but did not achieve biochemical control will begin their combination treatment of pasireotide at 0.3mg, 0.6mg or 0.9mg bid plus 0.5mg of cabergoline once a day at study entry. They will continue the treatment for 8 weeks. If biochemical control is not achieved at the end of the 8-week period, the dose of cabergoline will be increased to 1.0mg once a day and continue with the combination treatment for the remainder of 26 weeks.

If combination pasireotide and cabergoline 0.5mg once a day is not tolerated, the dose of cabergoline can be reduced to 0.5mg every other day. If 0.5mg every other day is not tolerated, and biochemical control is not achieved, patient should be considered for discontinuation if no clinical benefit is derived (see [Table 6-3](#)).

If combination pasireotide and cabergoline 1.0mg once a day is not tolerated, the dose of cabergoline can be reduced to 1.0mg every other day. If 1.0mg every other day is not tolerated, and biochemical control is not achieved, patient should be considered for discontinuation if no clinical benefit is derived (see [Table 6-3](#)).

The minimum treatment of any regimen is 8 weeks. Patients losing biochemical control at any time point after the 8-week treatment period at the starting combination dose will have the dose of the study medication increased immediately to the next level provided that the dose is well tolerated (see [Table 6-3](#)).

At week 9, before patient's UFC results are available, the investigator may select one of the following two options to dispense study medication to the patient for the next 26 weeks of treatment:

Option 1: The investigator dispenses study medication at the current dose, plus study medication at the next dose level at the end of week 8 visit. When patient's UFC results are available, the investigator should phone the patient to inform him/her to either remain at the current dose or titrate up to the next combination dose level.

Option 2: The investigator dispenses study medication at the current dose at the end of week 8 visit. When patient's UFC results are available and shown that his/her biochemical is not controlled, the investigator schedules a visit for patient to come to the clinic and pick up study medication at the next combination dose level.

**Table 6-3      Pasireotide and cabergoline dose modification steps for patients currently treated with maximal tolerated doses of pasireotide monotherapy**

Pasireotide: pasi Cabergoline: cabe	Starting dose level	Dose modification level - 1	Dose modification level - 2
Modification # 1	0.3, 0.6 or 0.9mg bid pasi + 0.5mg qd cabe <sup>a</sup>	0.3, 0.6 or 0.9mg bid pasi + 0.5mg every other day cabe <sup>a</sup>	Discontinuation if no clinical benefit
Modification # 2	0.3, 0.6 or 0.9mg bid pasi + 0.5mg qd cabe <sup>b</sup>	0.3, 0.6 or 0.9mg bid pasi + 1.0mg qd cabe <sup>a</sup>	
Modification # 3	0.3, 0.6 or 0.9mg bid pasi + 1.0mg qd cabe <sup>a</sup>	0.3, 0.6 or 0.9 mg bid pasi + 1.0mg every other day cabe <sup>a</sup>	0.3, 0.6 or 0.9mg bid pasi + 0.5mg qd cabe

<sup>a</sup> Dose modification is initiated if the current dose is not tolerated

<sup>b</sup> Dose modification is initiated if biochemical control is not achieved

## 6.5      Special safety

### 6.5.1    Hyperglycemia

Hyperglycemia is known to be associated with the treatment of somatostatin analogues. Clinical studies of pasireotide in healthy volunteers and in patients with Cushing's disease, acromegaly or carcinoid syndrome have reported transient, asymptomatic increases in fasting and postprandial glucose levels. Two clinical studies have been conducted [SOM230B2216] and [SOM230B2124] in healthy volunteers to further understand the mechanism of pasireotide-induced hyperglycemia and to evaluate the potential clinical utility of anti-diabetes agents in the management of pasireotide-induced hyperglycemia. Data from [SOM230B2216] study indicate that pasireotide decreases insulin secretion, particularly in the postprandial period, as well as the GLP-1/GIP secretion. Results from [SOM230B2124] study suggest that the incretin-based therapies (GLP-1 analogues and DPP-4 inhibitors) may have the best potential to manage the hyperglycemia associated with pasireotide. Some patients in [SOM230B2305] required insulin to treat their hyperglycemia.

### 6.5.2    Self-monitoring of blood glucose

The principal investigator is to educate the patient on the signs and symptoms of hyperglycemia. Patients must monitor their fasting blood glucose by finger stick at home at least 3 times per week for the first 4-week treatment with pasireotide or when the dose of pasireotide is increased. If a patient does not have any fasting values above 100mg/dL, monitoring can be decreased to at least 2 times per week from week 4 to week 12 and 1 time every week for the rest of the study. If glucose values remain normal (below 100mg/dL), monitoring is at the investigator's discretion during the extension phase (where it is applicable). If any values are observed above 100mg/dL, the guidelines in Figure 6-1 are to be followed. These guidelines are based on the current recommendations from the 2012 ADA and EASD aiming at a glycemic treatment goal of FPG < 130mg/dL (<7.2mmol/L). Appropriate actions such as initiation of anti-hyperglycemic therapy (and referral to diabetes specialist) are to be taken by the investigator as outlined on Figure 6-1. If fasting blood glucose values dictate initiation of anti-hyperglycemic treatment (i.e. confirmed > 130mg/dL by self-monitoring), a fasting plasma glucose sample using the central laboratory is to be

collected prior to initiation of anti-hyperglycemic treatment; however, treatment may be initiated using local laboratory results.

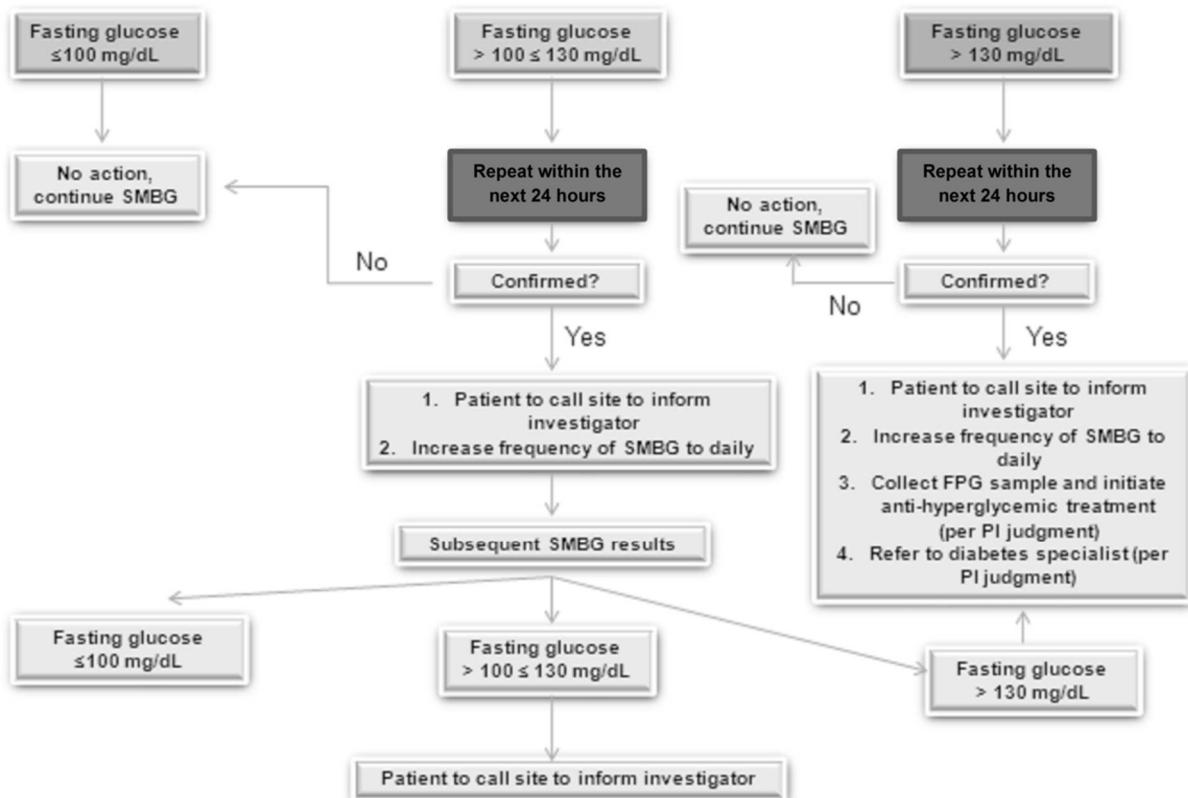
It is recommended that the patients be encouraged to keep a diary for their blood glucose for appropriate management throughout the study and present the collected data to their physician/diabetes specialist for evaluation. These data will not be collected by the sponsor.

In addition to self-monitoring, fasting plasma glucose and HbA<sub>1c</sub> will be collected at study visits per [Table 7-1](#) to [Table 7-4](#). Close and frequent monitoring of blood glucose is needed during pasireotide treatment. Intervention for hyperglycemia is to be implemented in any patient meeting any of the following criteria: FPG > 130mg/dL or HbA1c  $\geq$  6.5%.

Patients with FPG > 160mg/dL or HbA1c > 7.5% despite adjustment of antidiabetic therapy should be referred to a diabetes specialist (or earlier per investigator's judgment).

As outlined in [Table 6-4](#) patients with grade 3 hyperglycemia (FPG value > 250mg/dL; >13.9 mmol/L) at any point in the study should have the dose of pasireotide decreased. Patients who in spite of appropriate therapeutic interventions and despite dose reduction of study drug develop uncontrolled diabetes mellitus and/or consistently high blood glucose values: FPG  $\geq$  240mg/fdL (13.3 mmol/L) or HbA1c value  $\geq$  10% will require study treatment discontinuation.

**Figure 6-1 Fasting Self-Monitoring Blood Glucose guidelines**

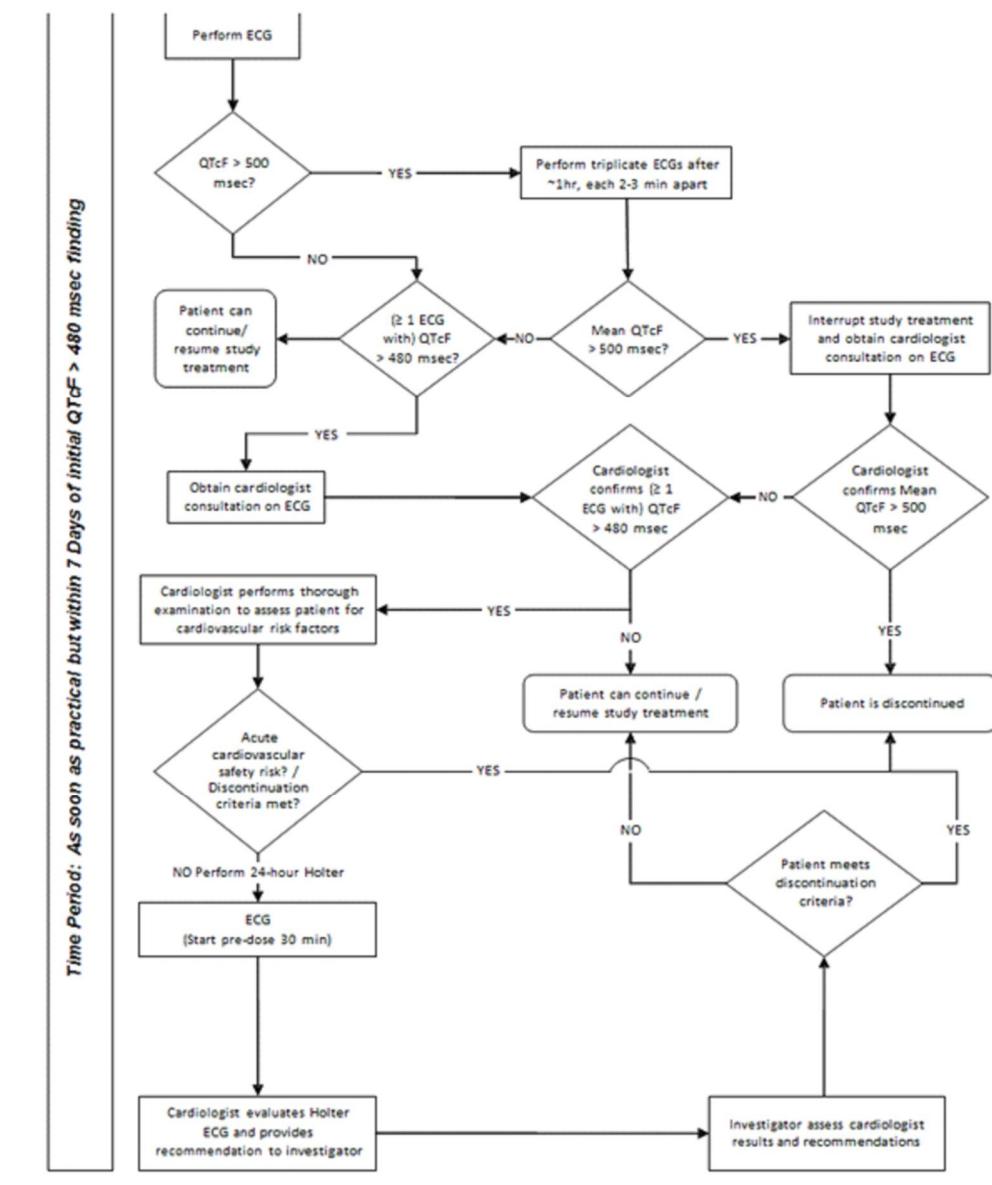


### 6.5.3 QT prolongation

If at any visit a QTcF>500 msec is observed, triplicate ECGs, each 2-3 min apart need to be taken approximately 1 hour after the initial ECG. The mean QTcF from the triplicate ECGs will be determined. If the mean QTcF is >500msec, the patient has to discontinue the study medication until a cardiologist has re-evaluated the ECG. The re-evaluation is required to be done as soon as practical but within 7 days of the initial finding of abnormal ECG. If the cardiologist confirms a mean QTcF >500msec, the patient will be withdrawn from the study. Otherwise and if the cardiologist confirms that at least one ECG shows QTcF >480msec, the cardiac assessments described for a confirmed QTcF >480msec are to be followed.

If at any visit a 480 msec > QTcF  $\leq$  500 msec is observed for the first time for a patient at a given dose level, the following steps are to be taken (as described in [Figure 6-2](#)):

- A cardiology consultation must be sought as soon as practical but within 7 days of the initial finding of abnormal ECG and the cardiologist is to re-evaluate the ECG
  - If a QTcF >480msec is NOT confirmed, no further action is to be taken
  - If a QTcF > 480msec is confirmed, a cardiologist must perform a thorough examination (such as reviewing baseline ECG, concurrent medications and performing a cardiovascular examination (including at least a cardiac auscultation) to assess the patient for cardiovascular risk factors).
    - If based upon the assessment by the cardiologist, the investigator considers that there is an acute cardiovascular safety risk and that the patient should not continue with study medication, the patient is to be discontinued immediately (discontinuation criteria to be followed).
    - If following the examination by the cardiologist, the investigator considers that there is not an acute cardiovascular safety risk and that the patient could continue to receive study medication, a 24-hr HolterECG is to be recorded as soon as practical but within 7 days after the initial finding of abnormal ECG. The Holter ECG is to be started 30 minutes prior to an injection of study medication.
    - The results of the ECGs, cardiac examination, Holter ECG and the recommendations by the cardiologist are to be evaluated by the Investigator to determine whether the patient should continue in the trial or not (discontinuation criteria to be followed)

**Figure 6-2 QT Prolongation monitoring flow chart**

#### 6.5.4 Hepatic Safety Management

Patients who develop increased transaminase and/or total bilirubin ( $> 2.0 \times \text{ULN}$ ) levels, should be monitored with a second liver function evaluation for confirmation. If confirmed, liver function should be frequently monitored until values return to pre-treatment levels.

If any of the criteria below are observed at any scheduled or unscheduled visit the sponsor should be notified immediately and the Hepatic Safety evaluation, described below, should be performed preferably within 48- hours of awareness of the abnormality:

Patient experiencing

- ALT or AST  $> 3 \times$  ULN and total bilirubin  $\geq 2 \times$  ULN
- ALT or AST  $> 5 \times$  ULN
- total bilirubin  $> 2.0 \times$  ULN

The following should be performed immediately within 72 hours of awareness of the abnormality:

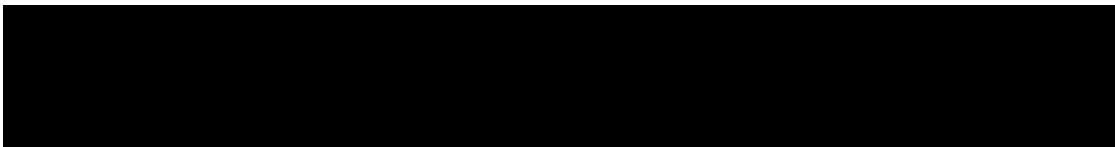
- Perform liver-directed medical history and physical examination (i.e. assess occupational hazards, concomitant medications including OTC meds, inter-current illness, etc.)
- Liver function tests: ALT, AST, total bilirubin, (fractionate to direct/indirect bilirubin if total bilirubin is  $> 2.0 \times$  ULN), Albumin, PT, INR, ALP, and GGT.
- Perform hepatitis screen: anti-HAV, IgM (to confirm acute Hepatitis A), HbsAg, Anti-HBc, anti-HCV (if positive, PCR viral load should be assessed), Anti-HEV, ANA antibodies, anti-smooth muscle anti-bodies, CMV and EBV
- Perform abdominal ultrasound (liver and biliary tree)

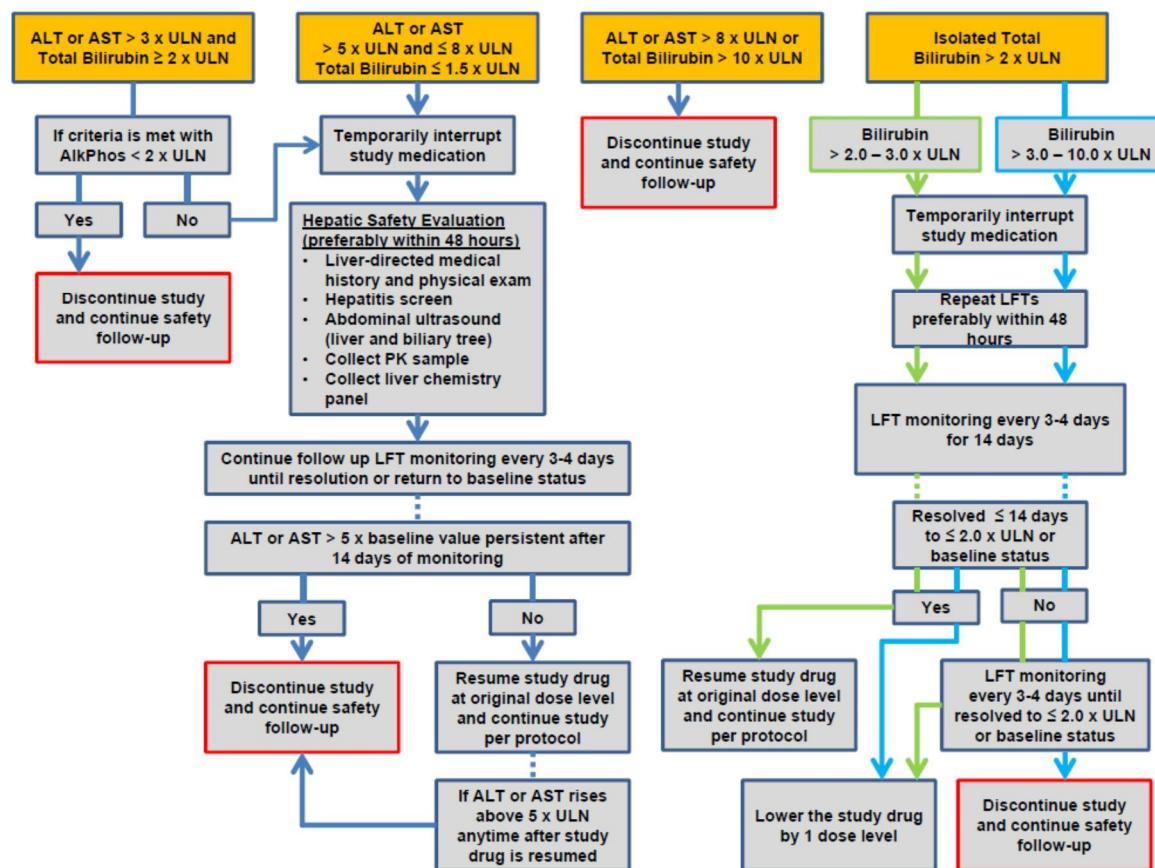
Liver function tests (LFTs) should be monitored every 3-4 days until resolution or return to baseline status.

Patients should be managed according to the LFT algorithm [Figure 6-3](#). Patients may need to be discontinued if the abnormal liver function criteria are met upon LFT retesting (See discontinuation criteria [Section 7.1.2.1](#)). Progress reports of the event should be maintained until resolution or stabilization (i.e. no further elevation after 2 consecutive assessments).

If any of these criteria are met and not confirmed by repeat testing, and the event is considered to be an adverse event by the investigator, the event must be recorded on the Adverse Event eCRF page; if the event is deemed serious by the investigator, then proceed with completing the SAE form. In addition, any significant findings from the physical examination should be recorded on the Adverse Event eCRF page.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified, should be considered as “medically significant”, thus, meet the definition of SAE ([Section 8.2.1](#)) and reported as SAE using the term “potential drug-induced liver injury”. All events should be followed up with the outcome clearly documented.



**Figure 6-3 LFT Management Algorithm**

## 6.6 Treatment interruption and treatment discontinuation

Patients experiencing unacceptable toxicity (AE grade 3 or higher) that the investigator considers directly attributable to pasireotide should have their dose reduced or should be withdrawn from the study. [Table 6-4](#) should be regarded as a guideline for the treatment of patients experiencing Adverse Events which are judged to be drug related. Any deviation from these guidelines should be discussed and approved by the sponsor.

If patients permanently discontinued from study treatment without completing the full 35 weeks of treatment in the core phase, the patients will be considered as prematurely discontinued from the study.

All patients must have a safety evaluation 28 days after the last dose of study treatment. Patients who do not complete study completions visit will be documented as a protocol deviation. This applies also to patients who discontinue the trial due to withdrawal of consent unless they do not consent to such a visit. Patients lost to follow up should be recorded as such on the CRF.

Adverse events are described as mild (Grade 1), moderate (Grade 2), severe (Grade 3) or life-threatening (Grade 4). Guidelines for treatment of patients experiencing adverse events are indicated below ([Table 6-4](#)).

**Table 6-4 Guidelines for treatment of patients experiencing adverse events**

Patients	Adverse Event	Action
All	AE grade $\leq$ 2 (mild to moderate)	No drug adjustments
	AE grade $\geq$ 3 (severe to life-threatening) and judged as pasireotide-related	Reduce dose of by 0.3mg bid. If AE improves to grade $\leq$ 2 within 1 week, increase dose by 0.3mg bid. If AE recurs at grade $\geq$ 3, reduce dose by 0.3mg bid again and remain at lower dose. If AE does not improve to grade $\leq$ 2 within 1 week on lower dose, reduce dose by 0.3mg bid again if possible. If AE does not improve to grade $\leq$ 2 within 1 week on 0.3mg bid patient should be discontinued from study treatment
	AE grade $\geq$ 3 (severe to life-threatening) and judged as cabergoline-related	Reduce dose from daily schedule to every other day schedule. If AE improves to grade $\leq$ 2 within 1 week, increase dose to daily schedule. If AE recurs at grade $\geq$ 3, reduce dose every other day schedule again and remain at that schedule. If AE does not improve to grade $\leq$ 2 within 1 week on the every other day schedule, patient should be discontinued from study treatment
	All patients	For patients experiencing hyperglycemia, the dose should be reduced if severity grade 3 or greater persists despite appropriate management. If the hyperglycemia is considered to be life-threatening, the patient should be withdrawn from study treatment regardless of anti-diabetes treatment
	AE grade 3 – All patients	NCI-CTCAE v4.03 grades diabetes that is treated with insulin as a grade 3. However, diabetes grade 3 will require a study drug dose reduction only in cases of uncontrolled hyperglycemia despite appropriate management. Patients who despite appropriate therapeutic interventions and dose reduction of study drug, develop uncontrolled diabetes and/or consistently high blood glucose values: FPG $\geq$ 240mg/fdL (13.3 mmol/L) or HbA1c value $\geq$ 10% will require study treatment discontinuation
	Hypocortisolism	If a patient shows high sensitivity to pasireotide 0.6 mg bid resulting in cortisol values $<$ LLN and/or signs/symptoms consistent with the diagnosis of hypocortisolism, the dose of pasireotide can be decreased to 0.3 mg bid. Despite the dose reduction, some patients may still present with cortisol values $<$ LLN and/or signs/symptoms consistent with hypocortisolism; in this case the dose of pasireotide can be further reduced to 0.3 mg qd in order to achieve and maintain normal cortisol levels.
No dose reductions are required in case of a QT prolongation but guidelines for QT monitoring and discontinuation criteria outlined in <a href="#">Section 6.5.3</a>		

## 6.7 Permitted concomitant therapy requiring caution and/or action

Patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug, as well as any changes in the dose of any medication the patient was taking prior to or during the study. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered during the study must be listed on the Concomitant Medications or the Procedures and Significant Non-Drug Therapies CRF, respectively. Diabetic patients must continue their treatment for diabetes throughout the study as indicated. If oral contraception is

used, the patient must have been practicing this method of birth control for at least three months prior to enrollment and must agree to continue the oral contraceptive throughout the course of the study and for 30 days after the last dose of study drug.

#### **6.7.1 Prohibited concomitant therapy**

PRAR $\gamma$  agonists (rosiglitazone or pioglitazone) treatment is not permitted during the study as it could affect patient's ACTH levels. Treatment with prednisolone is prohibited as this interferes with the UFC detection. Use of the medications listed in below that requires a washout are also prohibited during the study.

Further, the use of concomitant medications with a known risk for QT prolongation is prohibited and requires the discontinuation of the patient from the study prior to starting the respective QT prolonging medication. Please refer to [Appendix 4](#) for guidance regarding medications which pose a known risk for QT prolongation.

Patients on medical treatment for Cushing's disease the following washout periods must be completed before screening assessments are performed:

1. Inhibitors of steroidogenesis (ketoconazole, metyrapone): 1 week
2. Pituitary directed agents: Dopamine agonists (bromocriptine, cabergoline) and PPAR $\gamma$  agonists (rosiglitazone or pioglitazone): 4 weeks
3. Octreotide LAR, Lanreotide SR and Lanreotide autogel: 14 weeks
4. Octreotide (immediate release formulation): 1 week
5. Progesterone receptor antagonist (mifepristone): 4 weeks
6. Pasireotide s.c.: 2 weeks
7. Pasireotide LAR: 12 weeks

## **7 Study flow and visit schedule**

### **7.1 Study flow and visit schedule**

[Table 7-1](#) to [Table 7-4](#) list all of the assessments and indicate with an "x" where visits are performed. All data obtained from these assessments are recorded in the eCRF.



**Table 7-1 Core Phase - Visit evaluation schedule**

	Category	Protocol Section	Screening	Baseline (first dose)	Study Period											End of Treatment Visit (last dose)	Study Completion Visit ( Last dose + 28 days)		
					3	4	5	6	7	8	9	10	11	777	779				
<b>Visit Number</b>			1	2	3	4	5	6	7	8	9	10	11	777	779				
<b>Study Week</b>			-3 to 0	0	1	2	4	8	13	17	22	26	31	35					
Fasting Blood Glucose	D	7.2.2.5.2	x		x	x	x	x	x	x	x	x	x	x					
HbA1c	D	7.2.2.5.2	x				x		x				x		x				
Midnight salivary cortisol	D	7.2.1.3	x				x	x	x	x	x	x	x	x	x				
Urinary free cortisol and urine creatinine	D	7.2.1.1	x				x	x	x	x	x	x	x	x	x				
Serum cortisol	D	7.2.1.2	x			x	x	x	x	x	x	x	x	x	x				
Plasma ACTH	D	7.2.1.4	x			x	x	x	x	x	x	x	x	x	x				
HbsAg and anti-HCV	D	7.2.2.5.3	x																
Urinalysis	D	7.2.2.5.6	x						x				x	x	x				
Pregnancy Test	D	7.2.2.5.7	x	x	x	x	x	x	x	x	x	x	x	x	x				
<b>Imaging/Other assessments</b>																			
ECG (pasireotide pre-dose)	D	7.2.2.5.9	x	x	x	x	x	x	x	x	x	x	x	x	x				
Echocardiogram	D	7.2.2.5.10		x												x			
Gallbladder Ultrasound	D	7.2.2.5.8	x							x						x			
<b>Safety</b>																			
Adverse events	D	10.3.1.2														Continuous			
<b>Drug administration</b>	D	6														Continuous			

**Table 7-2 Extension Phase - Visit evaluation schedule**

	Category	Protocol Section	Study Period											End of Treatment Visit (last dose)	Study Completion Visit ( Last dose + 28 days)	
			13	14	15	16	17	18	19	20	21	22, 23...				
Visit Number			43	51	59	67	75	83	91	99	107	115, 123...	778	779		
Study Week														Last dose		
Imaging/Other assessments																
ECG (pasireotide pre-dose)	D	7.2.2.5.9	x	x	x	x	x	x	x	x	x	x	x	x		
Echocardiogram	D	7.2.2.5.10			x			x			x	x	x	x	x	
Gallbladder Ultrasound	D	7.2.2.5.8			x			x			x	x	x	x	x	
Safety																
Adverse events	D	10.3.1.2											Continuous			
Drug administration	D	6											Continuous			

Please refer to [Table 7-3](#) for extension phase assessment frequencies.

**Table 7-3 Extension Phase - Assessment frequencies**

Assessment	Frequency
Gallbladder	Every 6 months (24 weeks)
Hematology	Every 4 months (16 weeks)
GH and IGF-1	Every 4 months (16 weeks)
Free T4 and TSH	Every 6 months (24 weeks)
Blood chemistry	Every 4 months (16 weeks)
LFT	Every 2 months (8 weeks)
Coagulation	Every 4 months (16 weeks)
Fasting blood glucose	Every 2 months (8 weeks)
HbA1C	Every 4 months (16 weeks)
Midnight salivary cortisol	Every 2 months (8 weeks)
Urinary free cortisol and urine creatinine	Every 2 months (8 weeks)
Serum cortisol	Every 2 months (8 weeks)
Plasma ACTH	Every 2 months (8 weeks)
Signs and symptoms of Cushing's disease	Every 2 months (8 weeks)
Urinalysis	Every 4 months (16 weeks)
Pregnancy test	At every scheduled visit
ECG	Every 2 months (8 weeks)
Echocardiogram	Every 6 months (24 weeks)

**Table 7-4 Central Laboratory parameters collection plan**

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, MCH (Mean Corpuscular Hemoglobin), MCHC (Mean Cell Hemoglobin Concentration), MCV (Mean Corpuscular Volume), Platelets, Red blood cells, White blood cells, RBC Morphology with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)
Chemistry	Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), GGT, Calcium, Urine Creatinine, Creatine kinase, amylase, lipase, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, LDL- cholesterol, HDL-cholesterol, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, magnesium, sodium, potassium, serum creatinine, fasting blood glucose and glycosylated hemoglobin (HbA1C). Estimated glomerular filtration rate from serum creatinine at screening and end of treatment only
Urine collection	24 hour urinary collections for mUFC
Coagulation	International normalized ratio [INR] and Prothrombin time (PT)
Additional hormones	Midnight salivary cortisol, Urine free cortisol (UFC), Insulin-like growth factor 1 (IGF-1), GH, Free T4, and TSH, serum cortisol, Plasma ACTH
Pregnancy and assessments of fertility	All pre-menopausal women who are not surgically sterile will undergo a urine dip-stick - pregnancy test at visits indicated in <a href="#">Table 7-1</a> through <a href="#">Table 7-4</a> . The patient will be required to undergo a serum $\beta$ -hCG pregnancy test if the urine dip-stick pregnancy test is positive. A positive serum pregnancy test requires immediate interruption of study treatment until the assessment is confirmed. If positive, the patient must be discontinued from the study.

### **7.1.1 Screening**

The informed consent must be signed prior to ANY screening procedure being performed. Screening visit (Visit 1) should occur within 28 days prior to the baseline visit (Visit 2). The site should enter the Interactive Web Response System (IWRS) when a patient signs the informed consent and begins his/her screening. Patients that do not meet eligibility criteria are allowed to be rescreened and should use the same patient ID number. Rescreening should be documented in the source files.

If the following procedures meet all entry criteria at the original screening they do not have to be repeated for patients who rescreen within 60 days from the first day of the initial screening: vital signs, MRI, and gallbladder ultrasound. Any of these assessments that are abnormal and all other assessments not listed here are to be repeated.

#### **7.1.1.1 Enrollment and eligibility confirmation**

In order to determine and confirm the eligibility of the patient, when all screening procedures are completed, a key eligibility checklist must be completed in IWRS by the investigator or designee prior to receiving the first dose. After the eligibility has been checked and the patient is confirmed as eligible for the trial, the patient can then be enrolled for the trial.

#### **7.1.1.2 Information to be collected on screening failures**

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. The reason for screen fail will be entered on the appropriate CRF page. Screen failed patient's demographic information will still be recorded on the Demography CRF page. No other data will be entered into the clinical database for screen failed patients. Screening assessments of 24 hour urine free cortisol and late night salivary cortisol for patients who are screen failures will be collected by the central laboratory for analysis but no CRF page is to be completed. IWRS must be notified within 2 days of the screen fail.

#### **7.1.1.3 Patient demographics and other baseline characteristics**

Standard demographic information and medical history will be collected. Cushing's disease history and diabetes history together with the medication/treatment used will also be collected. Other baseline assessments will be collected as per [Table 7-1](#) and [Table 7-2](#).

#### **7.1.1.4 Treatment period – core phase**

The Study period in the core phase of the study is 35 weeks. Study visits are at week 1, week 2, week 4, week 8, week 13, week 17, week 22, week 26 week 31 and week 35. All visits should be performed within the indicated week (+/- 1 day).



### **7.1.2 End of treatment, including premature withdrawal and study discontinuation visit**

Patients who discontinue study treatment before visit 777 in the core phase and visit 778 in the extension phase, should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the EOT visit will be performed ([Table 7-1](#) and [Table 7-2](#)). An End of Treatment Phase Disposition CRF page should be completed, giving the date and reason for stopping the study treatment. At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 28 days following the last dose of study treatment.

If a study withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the End of Treatment Discontinuation CRF page. The investigator must contact IVRS to register the patient's discontinuation.

For criteria for premature withdrawal refer to Section 7.1.2.1.

#### **7.1.2.1 Criteria for premature patient withdrawal**

Patients **may** voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time.

Patients **must** be withdrawn from the study if any of the following occurs:

1. Patients experiencing unacceptable drug-related toxicity (as described in [Table 6-1](#))
2. Uncontrolled diabetes mellitus (DM), consistently high capillary glucose values in excess of 275 mg/dL (15.5 mmol/L), FPG  $\geq$  240 mg/dL (13.3 mmol/L) or HbA1c value  $\geq$  10 % despite prior appropriate management and prior dose adjustment of the study drug,
3. Patients experiencing adverse events in QTc:
  - a confirmed QTcF  $>$  480 msec and discontinuation recommended by a cardiologist, or
  - Mean QTcF  $>$  500 msec measured by triplicate ECGs and confirmed by a cardiologist
  - Significant arrhythmia findings from Holter monitoring such as:
    - a. Any ventricular or supra-ventricular tachyarrhythmia associated with symptoms of hemodynamic compromise
    - b. Sustained ventricular tachycardia ( $>$ 30 sec) irrespective of symptoms
    - c. Recurrent non-sustained VT ( $\geq$  3 beats) during any 24-hour monitoring period
    - d. Torsades de Pointes (TdP)
    - e. Cardiac arrest
    - f. Pause  $>$ 5 seconds
    - g. Second or third degree AV block
  - New occurrence of clinically significant/symptomatic bradycardia, or
  - Increased risk of QT prolongation by use of QT prolonging medication, or
  - Hypokalemia ( $<$ 3.5 mmol/L) or hypomagnesaemia ( $<$ 0.7 mmol/L) confirmed by repeat testing that is either a new finding or accompanied by vomiting or diarrhea and not corrected by treatment.

- Evidence of hypoadrenalinism: defined as an early morning (between 8 and 10 am) serum cortisol < 3 µg/dL and a UFC measurement < LLN or symptoms suggestive of hypoadrenalinism (e.g. postural hypotension, nausea, and abdominal pain) in association with a UFC measurement < LLN, which persist after drug dose adjustment
- Lack of efficacy: consistently elevated UFC level and lack of clinical benefit after  $\geq 3$  months treatment
- Pregnancy
- Patient experiencing
  - a. ALT or AST  $> 3 \times$  ULN and Total Bilirubin  $\geq 2 \times$  ULN and ALP  $< 2 \times$  ULN
  - b. ALT or AST  $> 5 \times$  ULN  $\leq 8 \times$  ULN persistent for more than 2 weeks
  - c. ALT or AST  $> 8 \times$  ULN

If any of those 3 discontinuation criteria are met, study medication should be discontinued immediately. In addition, proper safety follow up management should be performed as outline in [Section 6.5.4](#). Re-challenge of study medication is prohibited once discontinuation criteria are met.

If such withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the Study Completion CRF page. Patients may be withdrawn from the study prematurely for one of the following reasons:

1. Adverse event(s)
2. Abnormal laboratory value(s)
3. Abnormal test procedure result(s)
4. Protocol violation
5. Subject withdrew consent
6. Lost to follow-up
7. Administrative problems
8. Death

## 7.2 Assessment types

### 7.2.1 Efficacy assessments

#### 7.2.1.1 Mean urinary free cortisol (mUFC)

The primary efficacy parameter will be the proportion of patients who attain mUFC  $\leq 1.0$  ULN at week 35 with pasireotide alone or in combination with cabergoline.

Screening urinary free cortisol will be measured in three 24-hour urine specimens collected during the screening period 24-h urine collections will have to be performed within the first 8 to 10 days of the screening period so that to have 24h-UFC results available before visit 2 (baseline visit). The 24h-UFC concentration results from these three samples will be averaged to obtain the baseline urinary free cortisol level. During the study, mean 24h-UFC will be determined at 4 week interval in the core phase and at 8 week interval in the extension phase.



In the core phase of the study, patients at weeks 4, 8, 13, 17, 22, 26, 31 and 35, mean 24h-UFC will be determined from two 24-hour urine collections collected on two consecutive days occurring before the visit. In the extension phase of the study, patients' 24h-UFC will be determined at 8 week interval, at weeks 43, 51, 59, 67, 75 and so on. The 24h-UFC will continue to be determined from two 24-hour urine collections collected from two consecutive days occurring before the visit in the extension phase until patient is discontinued from treatment.

#### **7.2.1.2 Serum cortisol**

A pre-dose blood draw for an 8 am fasting serum cortisol measurement will be taken at visits indicated in [Table 7-1](#) and [Table 7-2](#). Procedures for sample drawing, handling, storage and transportation will be provided by the central laboratory.

#### **7.2.1.3 Late night salivary cortisol**

Late night salivary cortisol will be determined at visits indicated in [Table 7-1](#) and [Table 7-2](#).

Patients should be given instructions and supplies for use at home. In order to correlate the salivary and urinary cortisol results, a single salivary sample per evening is to be collected on the same evenings as the first 2 of the 3 twenty-four hour urinary collections for UFC for a total of 2 salivary samples as indicated in [Table 7-1](#) and [Table 7-2](#). One sample per evening is to be taken at 11 PM (23:00) with a +/- 1 hour window. All efforts should be made to have the samples taken at the same time throughout the study. Samples are to be collected by the site at the same time as the UFC samples as described in [Table 7-1](#) and [Table 7-2](#).

#### **7.2.1.4 Plasma ACTH**

A pre-dose blood draw for plasma ACTH sampling will be taken at visits indicated in [Table 7-1](#) and [Table 7-2](#). Procedures for sample drawing, handling, storage and transportation will be provided by the central laboratory.

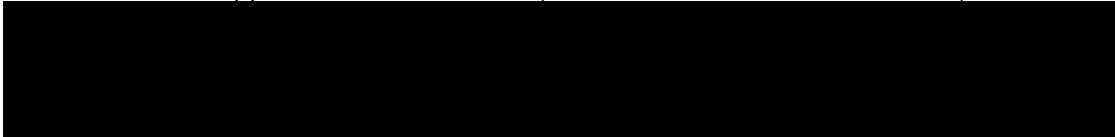
#### **7.2.1.5 Continuous measures of clinical symptoms of hypercortisolism**

The following clinical symptoms will be assessed:

##### **Manual Blood pressure:**

Sitting and standing blood pressure will be recorded at every indicated visit. The arm in which the highest sitting pressures are found at screening will be the arm used for all subsequent readings throughout the study. If there is a discrepancy between the arms regarding the highest systolic and diastolic value, the arm with the highest mean blood pressure will be used according to the following formula: mean BP = DBP + [(SBP – DBP)/3]. All attempts should be made to have the same individual obtain blood pressure readings from each individual patient at each visit at the same time of the day with the same equipment.

Arterial blood pressure determinations will be made in accordance with the (1988 AHA Committee Report) on blood pressure determination (Circulation 88: 2460-2467, 1993). With the arm supported at the level of the heart, systolic pressure will be recorded when the initial sound is heard (Phase I of the Korotkoff sound); diastolic pressure will be recorded at the disappearance of the sound (Phase V of the Korotkoff sound). At each study visit, after having



the patient in a sitting position for five minutes, systolic/diastolic blood pressure will be measured three times. The systolic/diastolic blood pressure will then be measured in a standing position three times. The repeat measurements are to be made at least at 5-minute intervals. No up-and-down rounding is allowed. The mean of all three sitting measurements is decisive for study specific procedures.

**Weight:** Body weight will be measured at every indicated visit using a calibrated balance. The balance should be placed on a hard flat surface, and checked for zero balance before each measurement. The patient should stand unassisted, in the center of the platform, and be asked to look straight ahead, standing relaxed but still. The patient should wear light underclothing and/or a paper examining gown and paper slippers. Shoes and socks should not be worn.

**Body mass index (BMI):**

BMI will be derived from the height and weight measurements

**Waist circumference:** Waist circumference will be measured at visits indicated in [Table 7-1](#) and [Table 7-2](#). Patients should remove clothing from around the waist to ensure the measuring tape is correctly positioned. Using a cosmetic pencil, make a mark at the “natural waist” midway between the palpated iliac crest and the palpated lowest rib margin in the left and right mid-axillary lines. Place the non-stretchable tape evenly around the natural waist covering the left and right natural-waist marks. The measurement scale should face outward, and there should be no twists in the tape. Ensure that the tape is just touching the skin but not compressing the soft tissue. Instruct patients to stand erect with abdomen relaxed, arms at sides, feet together, and weight divided equally over both legs.

#### **7.2.1.6 Categorical measures of clinical signs of hypercortisolism**

The results of all the following assessments will be recorded in the CRF.

The following symptoms will be evaluated using photographs taken at visits in the core and extension phases as indicated in [Table 7-1](#) and [Table 7-2](#):

**Facial rubor, hirsutism, striae, and supraclavicular and dorsal fat pad.** Two photographs, one frontal and one lateral from the shoulders up will be taken to assess facial plethora, supraclavicular and dorsal fat pads. Two photographs, frontal and dorsal of the trunk with patient in standing position will be taken to assess striae, and hirsutism. The photographs must be assessed by a qualified physician at the site, who is blinded to the dose given to the patient and to the time point at which the photographs were taken. Consisting with confidentiality requirements these will not be published without explicit written permission by the patient.

For further assessment of hirsutism, the Ferriman-Gallywey score (see [Appendix 5](#)), a method of evaluating and quantifying hirsutism in women, will be used. Female patients will be asked not to shave or use any methods of hair removal during the 3 weeks prior to corresponding visits if possible.



## **Muscle strength**

To test proximal muscle strength patients should be placed in a low seated position (for instance on an examination room stool). They should be asked to extend the arms in front of them. From this seated position patients will be asked to stand up. Patients will be evaluated using the following scale:

3. - completely unable to stand
2. - able to stand only by using arms as assistance
1. - able to stand after several efforts without using arms as assistance
0. - able to stand easily with arms extended

### **7.2.1.7 Health-related quality of life (HRQOL)**

The health-related quality of life will be assessed for patients using the Cushing QoL and SF-12v2 General Health Survey (see [Appendix 2](#) and [Appendix 3](#)), a patient-reported outcome instrument specific to patients with Cushing's syndrome. The questionnaires will be completed at visits indicated in [Table 7-1](#) and [Table 7-2](#).

## **7.2.2 Safety and tolerability assessments**

Safety will be monitored by assessing Physical examination, karnofsky performance status, vital signs, Laboratory assessments (hematology, chemistry, including LFTs, coagulation, urinalysis, hormone assessments, fasting blood glucose, HbA1C, GH and IGF-1), gallbladder ultrasound, and ECG as well as collecting of the adverse events at every visit.

### **7.2.2.1 Physical examination**

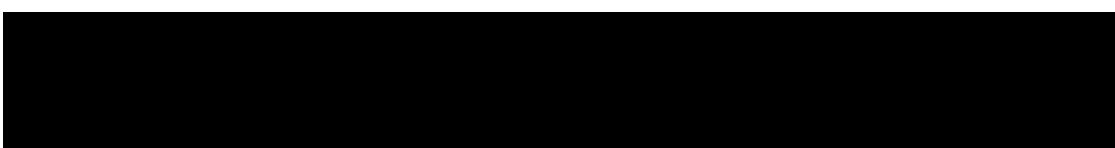
A complete physical examination will be performed by the investigator at screening visits indicated in [Table 7-1](#) and [Table 7-2](#). An abbreviated physical examination will be performed at the subsequent visits indicated [Table 7-1](#) and [Table 7-2](#). Information about the physical examination findings will be presented in the source documentation at the study site. Significant findings that were present prior to the signing of informed consent must be included in the Relevant Medical History/Current Medical Conditions page on the patient's CRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's CRF.

### **7.2.2.2 Vital signs**

Blood pressure, body temperature and heart rate will be measured visits indicated in [Table 7-1](#) and [Table 7-2](#) and recorded in the appropriate CRF.

### **7.2.2.3 Height and weight**

Height in centimeters (cm) and weight to the nearest 0.1 kilogram [kg] are to be collected at visits indicated in [Table 7-1](#) and [Table 7-2](#) and recorded in the appropriate CRF.



#### 7.2.2.4 Karnofsky performance status

The Karnofsky performance scale index (see [Appendix 1](#)) will be used to evaluate the performance status of the patients at visits indicated in [Table 7-1](#) and [Table 7-2](#).

#### 7.2.2.5 Laboratory evaluations

Central laboratories will be used for the analysis of all laboratory evaluations. Details on the collections, shipment of samples and reporting of results by the central laboratory are to be provided to investigators in the [\[Laboratory Manual\]](#).

##### 7.2.2.5.1 Hematology

Hematocrit, Hemoglobin, MCH, MCHC, MCV, Platelets, Red blood cells, White blood cells, RBC Morphology with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)

##### 7.2.2.5.2 Clinical chemistry

GGT, calcium, urine creatinine, creatine kinase, amylase, lipase, total cholesterol, LDL-cholesterol, HDL-cholesterol, total protein, triglycerides, blood urea nitrogen (BUN) or urea, uric acid, magnesium, sodium, potassium, serum creatinine, estimated glomerular filtration rate from serum creatinine (at screening and end of treatment only), fasting blood glucose and glycosylated hemoglobin (HbA1C).

The following Modification of Diet in Renal Disease (MDRD) will be used for creatinine clearance calculation:

MDRD (GFR) (ml/min/1.73m<sup>2</sup>) = 175 \* PD93 power -1.154 \* Age power - 0.203 \* Race \* Sex Where PD93 = Serum Creatinine (mg/dL), Race = 1.212 for Black & 1.000 for other, Sex = 1.00 for males and 0.742 for females.

SI Results MDRD (GFR) (ml/min/1.73m<sup>2</sup>) = 175 \* (PD9S3/88.4) power -1.154 \* Age power - 0.203 \* Race \* Sex Where PD9S3 = Serum Creatinine (UMOL/L), Race = 1.212 for Black & 1.000 for other, Sex = 1.00 for males and 0.742 for females.

##### 7.2.2.5.3 Liver function testing

Presence of HbsAg and Anti-HCV are to be assessed during screening. Liver function tests (LFTs) will be measured: ALT, AST, total bilirubin, direct bilirubin, indirect bilirubin, Albumin, ALP and GGT. If at any visit abnormal liver function criteria as described in the inclusion and exclusion section are met, the following should be performed immediately within 48 hours of awareness of the abnormality. Liver function tests (LFTs) should be monitored every 3-4 days until resolution or return to baseline status. Please refer to [Section 6.5.4 Hepatic Safety Management](#).

Perform hepatitis screen: anti-HAV, IgM (to confirm acute Hepatitis A), HbsAg, Anti-HBc, anti-HCV (if positive, PCR viral load should be assessed), Anti-HEV, ANA antibodies, anti-smooth muscle anti-bodies, CMV and EBV.

#### 7.2.2.5.4 Coagulation

PT and INR will be measured at visits indicated in [Table 7-1](#) and [Table 7-2](#).

#### 7.2.2.5.5 Additional hormones

Midnight salivary cortisol, Urine free cortisol (UFC), Insulin-like growth factor 1 (IGF-1), GH, Free T4, and TSH, serum cortisol, Plasma ACTH

#### 7.2.2.5.6 Urinalysis

A urinalysis test (specific gravity, pH, glucose, proteins, bilirubin, ketones, leucocytes, color, nitrite and blood) will be analyzed at visits indicated in [Table 7-1](#) and [Table 7-2](#). The 24 hour urinary collections used for mUFC will also be used to collect urine volume, and urinary creatinine.

#### 7.2.2.5.7 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have a urine dip-stick pregnancy test at visits indicated in [Table 7-1](#) and [Table 7-2](#). A serum  $\beta$ -hCG pregnancy test must be performed if the urine dip-stick pregnancy test is positive. A positive serum pregnancy test requires immediate interruption of study treatment until the assessment is confirmed. If positive, the patient must be discontinued from the study.

#### 7.2.2.5.8 Gallbladder ultrasound

A gallbladder ultrasound will be performed at the sites at visits indicated in [Table 7-1](#) and [Table 7-2](#) and the results will be recorded in the CRF.

#### 7.2.2.5.9 Cardiac assessments

##### Electrocardiogram (ECG)

A 12-lead ECG and a rhythm strip will be performed at the sites at visits indicated in [Table 7-1](#) and [Table 7-2](#). All ECGs should include all 12 standard leads and a Lead II rhythm strip of at least a 10- second duration. The ECGs will be performed on the machine(s) provided for the study by the central reader and are sent to the central reader for evaluation. To ensure consistency throughout all participating sites, the ECGs should be performed and processed following the guidelines from the central reading facility, which will be distributed to the sites. A Holter ECG will be required in case of a confirmed QTcF  $> 480$ msec (described in [Section 6.5.3](#)).

#### 7.2.2.5.10 Echocardiogram

An echocardiogram will be performed at the visits indicated in [Table 7-1](#) and [Table 7-2](#).



## 8 Safety monitoring and reporting

### 8.1 Adverse events

#### 8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained. Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected through a Death form.

The occurrence of adverse events should be sought by non-directive questioning of the patient during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (grade 1-4)
2. Its duration (start and end dates or Ongoing at End of Study)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a serious adverse even (SAE) is defined as in [Section 8.2.1](#)

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if

necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

All adverse events, regardless of the severity, should be reported. This will also include any adverse events that meet the definition of special interest.

### **8.1.2 Adverse events of special interest**

Adverse events of special interest consist of AEs for which there is a specific interest in connection with pasireotide treatment (i.e. where pasireotide may influence a common mechanism of action responsible for triggering them). The adverse events of special interest may require reporting additional information and completion of the event-specific checklists and/or questionnaires.

Targeted follow-up may be required for the following: hypocortisolism/cortisol withdrawal syndrome, hyperglycemia, and QTc interval prolongation.

### **8.1.3 Laboratory test abnormalities**

#### **8.1.3.1 Definitions and reporting**

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

## **8.2 Serious adverse events**

### **8.2.1 Definitions**

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

### **8.2.2 Reporting**

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the Novartis Chief Medical Office and Patient Safety (CMO&PS).

Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Chief Medical Office and Patient Safety (CMO&PS) department associate may



urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

### **8.3      Pregnancies**

To ensure patient safety, each pregnancy in a patient on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the investigator to the oncology Novartis Chief Medical Office and Patient Safety (CMO&PS) department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study treatment of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

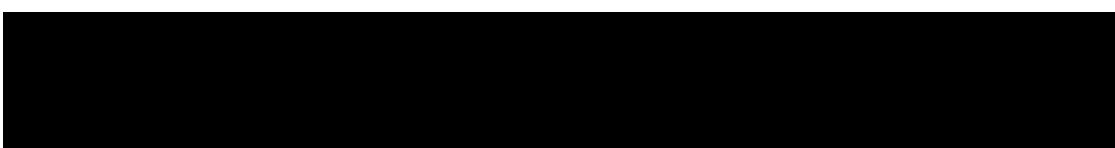
A newborn of a patient (or a partner of a patient) who becomes pregnant during the study within 1 month of the last pasireotide s.c. dose, should be followed for 3 months post-delivery (from Day 0 to Month 3 of life).

### **8.4      Warnings and precautions**

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided Investigator Brochure. Additional safety information collected between Investigator Brochure updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

### **8.5      Steering committee**

The steering committee will be established that will provide guidance for the analysis and the conduct of the study. It will consist of at least an independent medical expert in Cushing's disease, one study investigator and one Novartis physician. The roles and responsibilities of the Steering Committee will be defined in the Steering Committee Charter.



## 9 Data collection and management

### 9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

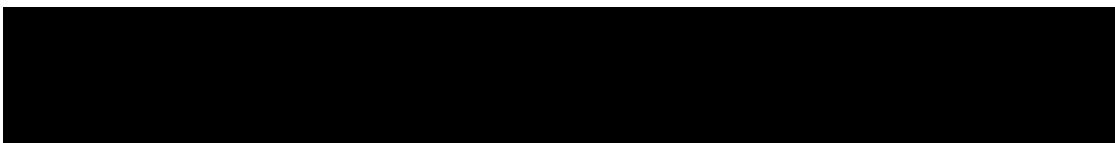
The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

Prior to entering key sensitive personally identifiable information (Subject Initials and exact Date of Birth), the system will prompt site to verify that this data is allowed to be collected. If the site indicates that country rules or ethics committee standards do not permit collection of these items, the system will not solicit Subject Initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the subject satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

### 9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on CRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).



The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

### **9.3 Data collection**

The designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

### **9.4 Database management and quality control**

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Samples and/or data will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

The investigator or designee should register a patient into the IVR and IWR system when a patient is screened, enrolled and discontinued from the study treatment. The IVR and IWR system will prompt the investigator to answer a few key inclusion/exclusion. When patient is discontinued from the study treatment, the status of study completion must be registered into the IVR and IWR system.

The occurrence of any protocol violations will be determined. After these actions have been completed and the data has been verified to be complete and accurate, the database will be declared locked. Authorization is required prior to making any database changes to locked data, by joint written agreement between the Global Head of Biostatistics and Data Management and the Global Head of Clinical Development.

For EDC studies, after database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.



## **10 Statistical methods and data analysis**

This is a phase II exploratory study to assess the efficacy and safety of pasireotide s.c. alone and in combination with cabergoline in patients with Cushing's disease.

The data will be analyzed by Novartis and/or designed CRO. It is planned that the data from all centers that participate in this protocol will be used.

Two separate analyses will be made one related to the core phase and one related to the overall phase, including the core and the extension phases.

Continuous variables will be summarized by number of patients, mean, standard deviation, minimum, 25<sup>th</sup> quantile, median, 75<sup>th</sup> quantile and maximum. Categorical variables will be summarized by absolute and relative frequencies.

Unless otherwise stated, baseline assessment refers to the last assessment prior to the patient's first study drug dose recorded after the signing of the informed consent.

In addition to the statistical methods outlined, further details and any additional exploratory analyses that may be performed will be described in the Statistical Analysis Plan (SAP).

### **10.1 Analysis sets**

#### **10.1.1 Full Analysis Set**

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned.

#### **10.1.2 Safety Set**

The Safety Set includes all patients who received at least one dose of study medication.

#### **10.1.3 Per-Protocol Set**

The Per-Protocol Set (PPS) consists of a subset of the patients in the FAS who received at least one dose of the study drug and had no major protocol violations. The protocol deviations criteria will be defined prior to database lock.

## **10.2 Patient demographics/other baseline characteristics**

Demographic and other baseline data will be summarized descriptively for the FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25<sup>th</sup> and 75<sup>th</sup> percentiles, minimum, and maximum will be presented.

#### **10.2.1 Treatments (study treatment, concomitant therapies, compliance)**

Descriptive statistics will be used to summarize the dose intensity and duration of drug exposure. The actual and planned doses administered and reason for dose change will be listed. Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized by ATC class and preferred term.

These analyses will be performed on the safety set.

### **10.2.2 Primary objective**

To evaluate the overall efficacy of the treatment regimen of pasireotide alone or in combination with cabergoline in patients with Cushing's disease with the proportion of patients who attain mUFC  $\leq$  1.0 ULN at week 35.

#### **10.2.2.1 Statistical hypothesis, model, and method of analysis**

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

- The proportion of patients with normalized mUFC at week 35 will be reported along with its corresponding asymptotic 95% CI.

### **10.2.3 Handling of missing values/censoring/discontinuations**

Patients missing mUFC at week 35, the last available mUFC assessment at or after week 31 will be carried forward as the week 35 mUFC assessment. However, if any patient discontinue between week 31 and week 35, then the patient's week-31 assessment will not be carried forward for week 35, and the week 35 mUFC assessment will be considered as non-response. Any patient who discontinue before week 31 will be considered as non-responder.

Sensitivity analyses may be performed using different methods for handling missing mUFC data to assess the robustness of the primary efficacy analysis. Details will be presented in the analysis plan.

### **10.2.4 Supportive analyses**

An additional analysis on the primary efficacy variable will also be performed using the PPS and the same handling of missing values as described above.

The primary efficacy endpoint at week 35 will be summarized by baseline mUFC categories.

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

### **10.3 Secondary objectives**

The secondary efficacy analysis will be performed on the FAS.

**Assess the changes in mUFC from baseline to study end at each scheduled visit where UFC is measured.**

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

**Assess overall efficacy of pasireotide alone or in combination with cabergoline as measured by normal mUFC levels at each scheduled visit.**

Proportion of patients with normalized mUFC (i.e. mUFC  $\leq$  1.0xULN) at each scheduled visit will be reported along with its corresponding 95% CI.

**Evaluate the overall efficacy of pasireotide alone or in combination with cabergoline as measured by controlled and partially controlled mUFC levels at each scheduled visit when mUFC is measured.**

Proportion of patients who attained mUFC  $\leq$  1.0 X ULN (controlled) or have at least 50% reduction (partially controlled) at each scheduled visit will be reported along with its corresponding 95% CI.

**Evaluate the duration of controlled or partially controlled mUFC response.**

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

**Assess the effect on plasma ACTH and serum cortisol.**

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

**Assess the effect of continuous measures of clinical symptoms of hypercortisolism.**

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

**Assess the effect on the categorical measures of clinical signs of hypercortisolism.**

Change in clinical signs of Cushing's disease: facial rubor, supraclavicular and dorsal fat pads, hirsutism, striae and muscle strength will be assessed using shift tables. Two assessors blinded to the visit number will score each qualitative endpoint (facial rubor, hirsutism, supraclavicular and dorsal fat pads and striae) by review of duplicated photographs. The investigator will adjudicate non-agreeing assessments. Table 10-1 below describes scales and endpoint definitions for each of these assessments. For each clinical sign, descriptive summary statistics will be presented.

**Table 10-1 Categorical clinical signs**

Clinical Symptom	Scale	Tool/Endpoint
Facial Rubor(redness)	0=none, 1=mild, 2=moderate,3=severe	Photographic interpretation, Count & percent shifts from baseline
Supraclavicular and dorsal fat pads	0=none, 1=mild, 2=moderate,3=severe	Photographic interpretation, Count & percent shifts from baseline
Hirsutism	Sum area scores to total body score,	Photographic interpretation, Descriptive % change from baseline
Striae	0=none, 1=mild, 2=moderate,3=severe	Photographic interpretation, Count & percent shifts from baseline
Muscle strength	0= minimum, 3= maximum	Direct observation of ability to stand unaided. Descriptive % change from baseline

### **Assess the improvement of health-related quality of life.**

Descriptive statistics, including mean, median, standard deviation, minimum and maximum, will be presented to describe actual standardized scores and changes from baseline. Graphical display(s) of descriptive results will be produced.

#### **10.3.1 Safety objectives**

##### **10.3.1.1 Analysis set and grouping for the analyses**

For all safety analyses, the safety set will be used. Key safety analyses will be presented for patients who receive pasireotide in combination with cabergoline after they started receiving the combination therapy.

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

1. pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
2. on-treatment period: from day of first dose of study medication to 28 days after last dose of study medication
3. post-treatment period: starting at day 28+1 after last dose of study medication.

##### **10.3.1.2 Adverse events (AEs)**

Summary tables for adverse events (AEs) have to include only AEs that started or worsened during the on-treatment period, the **treatment-emergent** AEs. However, all safety data (including those from the 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 adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on NCI-CTCAE v4.03 grades), type of adverse event, relation to study treatment. Similar summaries will also be produced for treatment-emergent AEs of special interest. The number and percentage of patients with at least one treatment-emergent Adverse Event of Special Interest will be reported.

Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event and treatment regimen.

Specific safety event categories (SEC) will be considered. Such categories consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment(s).

For each specified SEC, number and percentage of patients with at least one event part of the SEC will be reported.

#### **10.3.1.3 Laboratory abnormalities**

For laboratory tests covered by the National Cancer Institute - Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, the study's biostatistical and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, NCI-CTCAE v4.03 a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by NCI-CTCAE v4.03, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following summaries will be generated separately for hematology, biochemistry and urinary laboratory tests:

- shift tables using NCI-CTCAE v.4 grades to compare baseline to the worst on-treatment value
- for laboratory tests where NCI-CTCAE v4.03 grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.
- listing of all laboratory data with values flagged to show the corresponding NCI-CTCAE v4.03 grades and the classifications relative to the laboratory normal ranges.

In addition to the above mentioned tables and listings, other exploratory analyses, for example figures plotting time course of raw or change in laboratory tests over time or box plots might be specified in the MAP and/or SAP.

#### **10.3.1.4 Other safety data**

##### **ECG**

ECG data will be summarized with:

- shift table baseline to worst on-treatment result for overall assessments
- listing of ECG evaluations for all patients with at least one abnormality.

##### **Vital signs**

Vital signs (supine BP, HR & temperature) reporting of results will include:

- shift table baseline to worst on-treatment result
- table with descriptive statistics at baseline, one or several post-baseline time points and change from baseline to this/these post-baseline time points.

### **Karnofsky performance status**

Results will be summarized by visit using counts and percentages of

- patients in each performance status category.

### **Gallbladder Ultrasound**

Gallbladder data at each visit will be summarized and listed.

#### **10.3.1.5 Tolerability**

Tolerability will be studied in terms of dose reduction or drug interruption due to an AE.

[REDACTED]

#### **10.3.1.7 Patient-reported outcomes**

The health-related quality of life will be assessed for patients using the Cushing QoL, a Cushing's disease specific validated scale, and SF-12L, a generic QOL scale. These patient-reported outcome (PRO) measures are included as secondary endpoint in order to assess the beneficial clinical consequences of pasireotide LAR on disease specific and general QOL. Changes from baseline in the above outcomes measurements will be compared. PRO analysis of study data will be conducted on the subset of patients with all measurements. This analysis will utilize the previously defined Minimal Important Difference for Cushing QoL as well as correlations between Cushing QoL and SF-12 and both PRO instruments with UFC response and signs and symptoms of disease.

[REDACTED]

### **10.4 Interim analysis**

No formal interim analysis is planned for this study. If Novartis publishes interim data, details will be specified in the study's analysis plan. Interim analysis may be performed for regulatory purposes if deemed necessary.

[REDACTED]

However, an analysis of this trial will be performed at the end of the core phase, while the final analysis related to the overall phase, including the core and the extension phases, will be performed at the end of the extension phase after December 2019.

## **10.5 Sample size calculation**

The sample size was designed for the estimate of the proportions of patients with a normalized mUFC at week 35 in patients who are pasireotide untreated at screening or patients treated with pasireotide at screening but still with uncontrolled mUFC.

With a sample size of 64 patients and assuming that the proportion of patients who attain a mUFC  $\leq 1.0 \times \text{ULN}$  at week 35 will be 34 %, derived from a weighted mean of the original assumed response rates for Group 1 (35%) and 2 (28%) and assuming that a maximum of 6 out of 64 patients (approx. 10 %) will be enrolled in Group 2, the precision of the response will be 12.8 % for the associated two-sided 95% CI considering a drop-out rate of 10%.

# **11 Ethical considerations and administrative procedures**

## **11.1 Regulatory and ethical compliance**

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

## **11.2 Responsibilities of the investigator and IRB/IEC/REB**

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

## **11.3 Informed consent procedures**

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their CRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator

must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

## **11.4 Discontinuation of the study**

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in [Section 7.1.2.1](#).

### **Publication of study protocol and results**

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

#### **11.4.1 Communication and Publication of Clinical Trial Results**

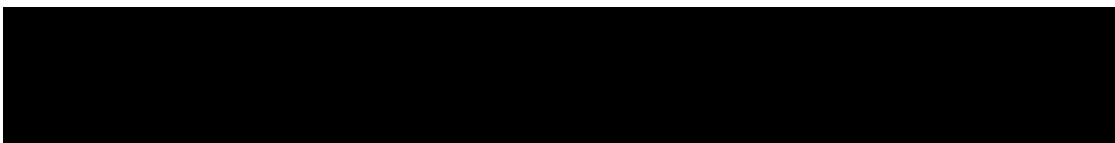
Novartis is committed to upholding the highest ethical standards for reporting the results of medical research, including the timely communication and publication of clinical trials results, whatever their outcome.

Novartis complies with the authorship guidelines of the International Committee of Medical Journal Editors (ICMJE) uniform requirements for manuscripts submitted to biomedical journals and other specific guidelines of the journal or congress to which the document will be submitted. These guidelines apply to any clinical trial publication including but not limited to manuscripts, abstracts, posters, and oral presentations. For more information regarding the ICMJE guidelines, visit <http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html>.

Accordingly, all authors must have:

- Contributed substantially to the study concept, design and/or conduct of the study or to the acquisition, analysis, and interpretation of the data AND
- Drafted or critically revised the proposed clinical publication for important intellectual content AND
- Approved the final proposed clinical publication for submission AND
- Have intimate knowledge of trial implementation/analysis

Substantial contribution for primary publication is defined as having active and ongoing participation in the study. Study steering committee members must have significant involvement to study concept, design, and data interpretation and patient recruitment. Each steering committee member must have attended the majority of the steering committee meetings and recruited patients into the trial from his/her own center to be included as an



author. Study investigators must have significant contribution to patient recruitment based on number of eligible patients upon study entry and data quality.

## **11.5 Study documentation, record keeping and retention of documents**

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The CRF is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.



## **11.6 Confidentiality of study documents and patient records**

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

## **11.7 Audits and inspections**

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

## **11.8 Financial disclosures**

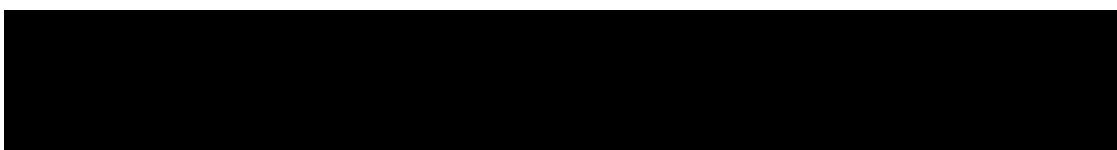
Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

# **12 Protocol adherence**

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

## **12.1 Amendments to the protocol**

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.



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## 14 Appendices

### 14.1 Appendix 1 Karnofsky performance status

#### Performance status:

- 100. - Normal, no complaints
- 90. - Able to carry on normal activity, minor signs or symptoms of disease
- 80. - Normal activity with effort; some signs or symptoms of disease
- 70. - Cares for self; unable to carry on normal activity or do active work
- 60. - Requires occasional assistance but is able to care for most of his needs
- 50. - Requires considerable assistance and frequent medical care
- 40. - Disabled, requires special care and assistance
- 30. - Severely disabled; hospitalization is indicated though death not imminent
- 20. - Very sick; hospitalization is necessary; active support treatment is necessary
- 10. - Moribund; fatal processes progressing rapidly
- 0. - Dead

## 14.2 Appendix 2: Cushing's Syndrome Quality of Life Questionnaire

 NOVARTIS		Page 4001	
<b>PROTOCOL NAME OR NO TRIAL CODE</b>	<b>ID</b>	Center No.	Subject No.
		Subject's initials	1. 2. fam.
		Visit Date	day month year
		Visit # _____	

### CUSHING'S SYNDROME QUALITY OF LIFE QUESTIONNAIRE (CUSHINGQoL QUESTIONNAIRE)

The following sentences refer to what you may think or feel about your Cushing's syndrome. Your answers will help us to know how you feel and how much your illness has interfered in your usual activities in **the past 4 weeks**.

Below each sentence you will find several response choices. Please read each sentence carefully. After reading each sentence, check the box next to the answer that best describes what you think is happening to you.

There are **NO** right or wrong answers. We are simply interested in what is happening to you because of your Cushing's syndrome.

1. I have trouble sleeping (I wake up during the night; it takes me a long time to get to sleep, etc.).

- Always
- Often
- Sometimes
- Rarely
- Never

2. I have pain that keeps me from leading a normal life.

- Always
- Often
- Sometimes
- Rarely
- Never

 NOVARTIS

<b>PROTOCOL NAME OR NO</b>	<b>ID</b>	Center No. <input type="text"/>	Subject No. <input type="text"/>
<b>TRIAL CODE</b>	Subject's Initials <input type="text"/>	1. <input type="text"/>	2. <input type="text"/> fam.
		Visit # <input type="text"/>	

Page 4002

3. My wounds take a long time to heal.

- Always
- Often
- Sometimes
- Rarely
- Never

4. I bruise easily.

- Always
- Often
- Sometimes
- Rarely
- Never

5. I am more irritable, I have sudden mood swings and angry outbursts.

- Always
- Often
- Sometimes
- Rarely
- Never

6. I have less self-confidence, I feel more insecure.

- Always
- Often
- Sometimes
- Rarely
- Never

 NOVARTIS

<b>PROTOCOL NAME OR NO TRIAL CODE</b>	<b>ID</b>	<input type="text"/> Center No.	<input type="text"/> Subject No.
	Subject's initials	<input type="text"/> <input type="text"/>	1. 2. fam.
			<b>Visit #</b> <input type="text"/>

Page 4003

7. I'm worried about the changes in my physical appearance due to my illness.

- Very much
- Quite a bit
- Somewhat
- Very little
- Not at all

8. I feel less like going out or seeing relatives or friends.

- Always
- Often
- Sometimes
- Rarely
- Never

9. I have had to give up my social or leisure activities due to my illness.

- Always
- Often
- Sometimes
- Rarely
- Never

10. My illness affects my everyday activities such as working or studying.

- Always
- Often
- Sometimes
- Rarely
- Never

 NOVARTIS

<b>PROTOCOL NAME OR NO TRIAL CODE</b>	<b>ID</b> Center No. _____ Subject No. _____ Subject's initials _____ 1. 2. fam.	Page 4004 Visit # _____
---	--	----------------------------

11. It's difficult for me to remember things.

- Always
- Often
- Sometimes
- Rarely
- Never

12. I'm worried about my health in the future.

- Very much
- Quite a bit
- Somewhat
- Very little
- Not at all

## 14.3 Appendix 3 Patient Report Outcome Questionnaire - SF 12 - v2

 <b>NOVARTIS</b>		Page 4001
<b>PROTOCOL NAME OR NO TRIAL CODE</b>	<b>ID</b> Center No. _____ Subject No. _____  Subject's initials _____  Visit Date _____ 1. 2. fam. day month year	Visit # _____

Your Health and Well-Being																			
<p>This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. <i>Thank you for completing this survey!</i></p> <p>For each of the following questions, please mark an <input type="checkbox"/> in the one box that best describes your answer.</p>																			
<p><b>1. In general, would you say your health is:</b></p> <table border="1" style="margin-left: auto; margin-right: auto; border-collapse: collapse;"> <tr> <td style="padding: 2px;">Excellent</td> <td style="padding: 2px;">Very good</td> <td style="padding: 2px;">Good</td> <td style="padding: 2px;">Fair</td> <td style="padding: 2px;">Poor</td> </tr> <tr> <td style="text-align: center; padding: 2px;">▼</td> </tr> <tr> <td style="text-align: center; padding: 2px;"><input type="checkbox"/> 1</td> <td style="text-align: center; padding: 2px;"><input type="checkbox"/> 2</td> <td style="text-align: center; padding: 2px;"><input type="checkbox"/> 3</td> <td style="text-align: center; padding: 2px;"><input type="checkbox"/> 4</td> <td style="text-align: center; padding: 2px;"><input type="checkbox"/> 5</td> </tr> </table>					Excellent	Very good	Good	Fair	Poor	▼	▼	▼	▼	▼	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
Excellent	Very good	Good	Fair	Poor															
▼	▼	▼	▼	▼															
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5															
<p><b>2. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?</b></p> <table border="1" style="margin-left: auto; margin-right: auto; border-collapse: collapse;"> <tr> <td style="padding: 2px; text-align: center;">Yes, limited a lot</td> <td style="padding: 2px; text-align: center;">Yes, limited a little</td> <td style="padding: 2px; text-align: center;">No, not limited at all</td> </tr> <tr> <td style="text-align: center; padding: 2px;">▼</td> <td style="text-align: center; padding: 2px;">▼</td> <td style="text-align: center; padding: 2px;">▼</td> </tr> </table> <p>• <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf ..... <input type="checkbox"/> 1 ..... <input type="checkbox"/> 2 ..... <input type="checkbox"/> 3</p> <p>• Climbing <u>several</u> flights of stairs ..... <input type="checkbox"/> 1 ..... <input type="checkbox"/> 2 ..... <input type="checkbox"/> 3</p>					Yes, limited a lot	Yes, limited a little	No, not limited at all	▼	▼	▼									
Yes, limited a lot	Yes, limited a little	No, not limited at all																	
▼	▼	▼																	
<p>SF-12v2® Health Survey © 1994, 2002 Medical Outcomes Trust and QualityMetric Incorporated. All rights reserved.            SF-12® is a registered trademark of Medical Outcomes Trust.            (SF-12v2® Health Survey Standard, United States (English))</p>																			

**NOVARTIS**

<b>PROTOCOL NAME OR NO TRIAL CODE</b>	<b>ID</b>	Center No.	Subject No.
	Subject's initials	1. <input type="text"/>	2. <input type="text"/>

Page 4002

Visit #

3. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
<input type="text"/>				

a) Accomplished less than you would like.....  1 .....  2 .....  3 .....  4 .....  5

b) Were limited in the kind of work or other activities.....  1 .....  2 .....  3 .....  4 .....  5

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
<input type="text"/>				

a) Accomplished less than you would like.....  1 .....  2 .....  3 .....  4 .....  5

b) Did work or other activities less carefully than usual.....  1 .....  2 .....  3 .....  4 .....  5

5. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
<input type="text"/>				
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

**NOVARTIS**

<b>PROTOCOL NAME OR NO TRIAL CODE</b>	<b>ID</b> Center No. _____ Subject No. _____	Page 4003
	Subject's initials _____ 1. 2. fam.	Visit # _____

6. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼

a Have you felt calm and peaceful? .....  1 .....  2 .....  3 .....  4 .....  5

b Did you have a lot of energy? .....  1 .....  2 .....  3 .....  4 .....  5

c Have you felt downhearted and depressed? .....  1 .....  2 .....  3 .....  4 .....  5

7. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

*Thank you for completing these questions!*

**14.4 Appendix 4: Medications known to be associated with QT interval prolongation**

The following link contains a list of drugs generally recognized to have a possible association with QT prolongation:

<https://www.crediblemeds.org/index.php/login/dlcheck>

#### **14.5 Appendix 5: Ferriman-Gallwey Score**

The Ferriman-Gallwey scoring system is used to score the degree of excess male pattern body hair in females. A score is to be assigned for each body location pictured below (upper lip, chin, chest, upper abdomen, lower abdomen, arms, thighs, upper back and lower back) and then added together to get the total score (see [Figure 14-1](#)). The definition of each grade is listed here:

4. - extensive terminal hair growth
3. - moderate terminal hair growth
2. - mild terminal hair growth
1. - no excessive terminal hair growth
0. - absence of terminal hair growth

**Figure 14-1 Ferriman-Gallwey Scoring Diagram**