



Clinical Development & Medical Affairs

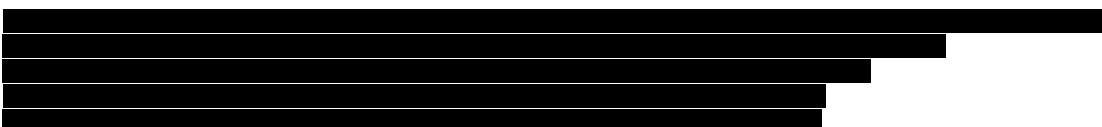
SOM230 (Pasireotide)

Clinical Trial Protocol CSOM230B2406 / NCT01582061

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

	
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## Protocol Summary

### Study title:

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

### Study phase:

IIIb

### Study objectives:

#### Primary objective:

- To document the safety of pasireotide s.c. in patients with Cushing's Disease (CD).

#### Secondary objectives:

- To document the efficacy of pasireotide s.c. in normalizing mean 24h-UFC at Week 12, 24 and 48, separately,
- To document the efficacy of pasireotide s.c. in achieving at least 50% reduction of mean 24h-UFC from baseline at Week 12, 24 and 48, separately,
- To document the changes in clinical signs and symptoms,
- To document the changes in patient-reported outcome questionnaires (CushingQoL and WPAI-GH),
- To document the effects of pasireotide s.c. on the GH/IGF-I axis,
- To document the overall safety and tolerability of pasireotide s.c. in patients with CD.

### Study population:

Patients with persistent or recurrent Cushing's disease or patients with de novo Cushing's disease that are not considered candidates for pituitary surgery. A confirmed Cushing's disease is required.

### Key inclusion criteria:

Patients with confirmed diagnosis of Cushing's disease as evidenced by mean 24h-UFC > ULN, normal or above normal morning plasma ACTH and MRI or IPSS, patients with de novo Cushing's disease must not be considered candidates for pituitary surgery (i.e. poor surgical candidates, surgically unapproachable tumors, patients with no visible pituitary tumor, patients who refuse to have surgical treatment). Karnofsky performance status > 60.

### Key exclusion criteria:

Radiotherapy of the pituitary < 4 weeks before screening or patient who has not recovered from side effects, compression of the optic chiasm causing acute clinically significant visual field defect, Cushing's syndrome due to ectopic ACTH secretion, hypercortisolism secondary to adrenal tumors or nodular (primary) bilateral adrenal hyperplasia, patients who have a known inherited syndrome as the cause for hormone over secretion, diagnosis of glucocorticoid-remedial aldosteronism (GRA), symptomatic cholelithiasis, symptomatic bile duct dilation, acute or chronic pancreatitis, diabetes patients whose fasting blood glucose is poorly controlled as evidenced by HbA<sub>1C</sub> > 8%, clinically significant impairment in cardiovascular function or risk thereof, liver disease, patients with presence of Hepatitis B surface antigen, patients with presence of Hepatitis C antibody test, female patients pregnant or lactating, or of childbearing potential and not practicing a medically acceptable method of birth control.

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**Number of patients:**

The estimated sample size is 200 patients. The actual sample size may differ from this planned number.

**Overview of study design:**

This is an open-label, uncontrolled, single-arm, multi-center, multi-national expanded access study.

The starting dose will be:

- **[Applicable for countries in the European Union]** 600 µg b.i.d. (twice daily) in all patients also including the ones with impaired glucose metabolism with the option to increase the dose to 900 µg b.i.d. if the patient is not controlled (i.e. 24h-mean UFC levels above the upper limit of normal) at earliest after 2 months of treatment provided the 600 µg b.i.d dose is well tolerated by the patient. Ongoing patients in the study at the time of approval of amendment 3 will continue on their current dose.
- **[Applicable for countries outside the European Union]** 900 µg b.i.d. (twice daily). The initial dose for patients with impaired glucose metabolism will be 600 µg b.i.d

Refer to [Section 6.2.1](#) for allowed dose modifications.

After a 21-day screening period, patients who satisfy all the inclusion/exclusion criteria will start receiving pasireotide s.c. twice a day. During the first 24-week period, patients will have a visit on a weekly basis up to week 4 and will then be followed on a 4-week basis up to week 24. In the second study period, patients will be followed at 12-week intervals until the end of the study.

Patients will be treated until pasireotide is approved for commercial use and reimbursed in each respective country or until 31 December 2015 (until 31 December 2016 for sites in South Korea and Brazil), whichever occurs first.

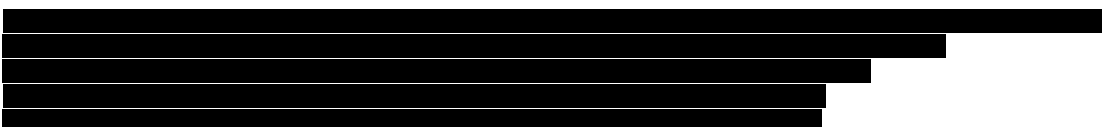
**Statistical considerations:**

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

**Secondary endpoints:**

- The proportion of patients with mean 24h-UFC  $\leq$  ULN at Week 12, 24 and 48, separately,
- The proportion of patients achieving a reduction of mean 24h-UFC  $\geq$  50% from baseline at Week 12, 24 and 48, separately,
- The change from baseline to Week 12, 24 and 48 in clinical signs and symptoms,
- The change from baseline to Week 12, 24 and 48 in CushingQoL and WPAI-GH scores,
- The change from baseline to Week 12, 24 and 48 in GH and IGF-I separately,
- Incidence of AEs, and laboratory, vital signs and electrocardiographic abnormalities. Changes in laboratory values, electrocardiograms readings, and in vital signs values.

Categorical data will be presented as frequencies and percentages (with corresponding two-sided 95% CI, as appropriate). For continuous data, the mean, standard deviation, median, minimum, and maximum will be presented.



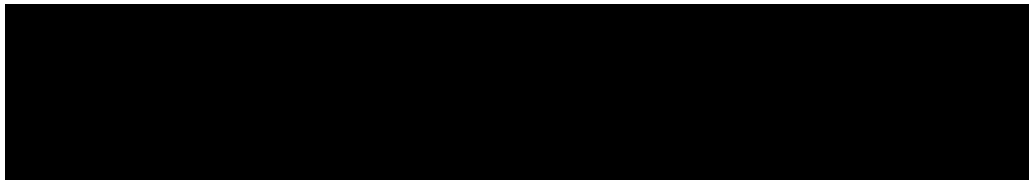
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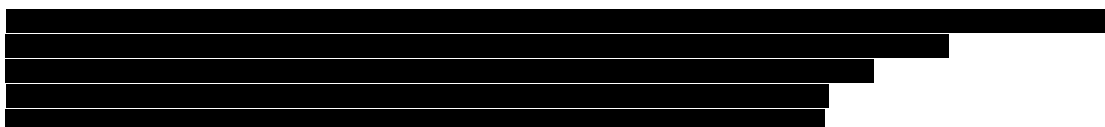
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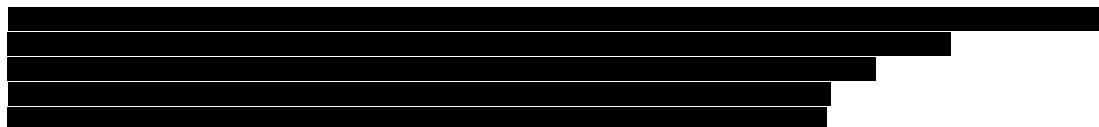


## List of abbreviations

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ACTH	Adrenocorticotrophic hormone
ADA	American Diabetes Association
AE	Adverse Event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ALP	Alkaline Phosphatase
ANA	Antinuclear antibody
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
b.i.d.	bis in diem/twice a day
BIPSS	Bilateral inferior petrosal sinus sampling
BMI	Body mass index
cAMP	Cyclic adenosine monophosphate
CD	Cushing's disease
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMV	Cytomegalovirus
CRF	Case Report/Record Form
CRH	Corticotrophin-releasing hormone
CRO	Contract Research Organization
CS&E	Clinical Safety and Epidemiology
CSR	Clinical study report
CSR addendum	An addendum to Clinical Study Report (CSR) that captures all the additional information that is not included in the CSR
CTCAE	Common Terminology Criteria for Adverse Events
CTH	Clinical Trial Head
DDAVP	1-Desamino-8-D-Arginin-Vasopressin (Desmopressin)
DM	Diabetes mellitus
DS&E	Drug Safety and Epidemiology
EASD	European Association for the Study of Diabetes
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ELISA	Enzyme Linked Immunosorbent Assay
FPFV	First patient first visit
FPG	Fasting Plasma Glucose
FU	Follow-up
GEP/NET	Gastroenteropancreatic neuroendocrine tumors
GGT	Gamma Glutamyl Transferase
GRA	Glucocorticoid-Remedial Aldosteronism
Gsa/Gsp	Alpha-subunit of the GTP-binding protein (non mutated/mutated)
HAV	Hepatitis A virus
HBc	Hepatitis B core
HbsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus

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HEV	Hepatitis E virus
HIV	Human Immunodeficiency Virus
HPLC	High pressure liquid chromatography
HRQoL	Health-related quality of life
IgM	Immunoglobulin M
i.v.	intravenous(ly)
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
INR	International normalized ratio
IPSS	Inferior petrosal sinus sampling
IRB	Institutional Review Board
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
IVRS	Interactive Voice Response System
LAR	Long-acting release
LDDST	Low-dose dexamethasone suppression test
LDL	Low density lipoprotein
LFT	Liver Function Testing
LLN	Lower limit normal
LPLV	Last patient last visit
MAP	Master Analysis Plan documents project standards in the statistical methods which will be used within the individual clinical trial RAP documentation
MEN-1	Multiple Endocrine Neoplasia type-1
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NYHA	New York Heart Association
OTC	Over the counter medication
PCR	Polymerase Chain Reaction
PLT	Platelets
POC	Proof of Concept
PPG	Post-Prandial capillary Glucose
PT	Prothrombin time
PTT	Partial thromboplastin time
QoL	Quality of Life
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
REB	Research Ethics Board
SAE	Serious Adverse Event
s.c.	Sub-cutaneous
SOP	Standard Operating Procedure
SR	Slow release
SRIFa	Somatostatin analog

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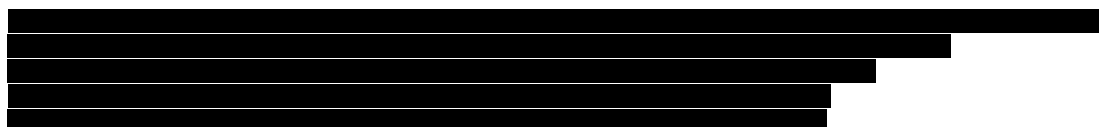
SSA	Somatostatin Analogs
SSC	Study Steering Committee
Sst	Somatostatin receptors
TC	Total Cholesterol
TdP	Torsades de Pointe
TSH	Thyrotropic hormone
UFC	Urinary free cortisol
ULN	Upper limit normal
WBC	White blood cells
WPAI-GH	Work Productivity and Activity Impairment-General Health

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## Glossary of terms

Assessment	A procedure used to generate data required by the study
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 testing 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
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Subject Number (Subject No.)	A unique identifying number assigned to each patient who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
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
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
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints



## **Amendment 6**

### **Amendment rationale**

This protocol is being amended:

The current version of the study ends on 31 December 2015. Two participating countries, Brazil and South Korea, have not yet received pasireotide approval and reimbursement. To continue to provide access to these countries, the protocol has been extended to 31 December 2016, for these 2 countries only.

### **Changes to the protocol**

Changes to specific sections of the protocol are shown in the track changes version of the protocol.

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

- Study duration is extended from 31 December 2015 to 31 December 2016 throughout the protocol for Brazil and South Korea.

### **IRB/IEC/REB Approval**

A copy of this amended protocol must 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 5

### Amendment rationale

This protocol is being amended:

Upon review of the program details for B2406 it was identified that this protocol was registered as a Phase IIIb clinical trial.

Non-serious adverse event collection in the safety database is only required for expanded treatment programs not registered as clinical trials with the Health Authorities. Therefore, monthly reporting of non-serious adverse events has been removed from this protocol amendment.

In recent months new standard language has been developed for the Inclusion/Exclusion Criteria checklists. It is required now that sites must complete an Inclusion/Exclusion criteria checklist and submit it to Novartis for an approval prior to enrolling new patients into the trial. The relevant language was added to the protocol.

This amended version of the protocol now states that an Interim Analysis may be performed per health authority requests or for publication purpose.

Lastly, this amended version of the protocol contains new standard safety language regarding QT prolonging medications. All reference to medications that *might* lead to QT prolongation has been re-worded to state “medication with known risk of TdP”.

### Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol.

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

- Section 4.2 - updated this section to include wording that the Interim analysis may be used for publications purposes in addition to HA purposes.
- Sections 5.3, 6.3.2 and 7.1.3.1 - Changed wording, “medication that might lead to QT Prolongation” to “medication with known risk of TdP” and also updated the link to the referenced website
- Table 7-1 - Added completion of the inclusion / exclusion criteria checklist to the visit schedule at screening
- Section 7.1.1 - Enrollment and eligibility confirmation section was added to describe the inclusion / exclusion criteria checklist in more detail
- Section 10.7 - Added Interim Analysis may be performed for Health Authority purpose or for publication purpose.
- Section 8.2.2 - Removed monthly AE reporting language

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[REDACTED]

[REDACTED]



**IRB/IEC/REB Approval**

A copy of this amended protocol must 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 4

### Amendment rationale

This protocol is being amended:

To be in compliance with the standard maximum half-life of mifepristone s.c. of approximately 12 hours as indicated in the US Prescribing Information, the amendment has extended the washout period of mifepristone from one to four weeks in inclusion criterion #6. As the SOM program has recently standardized the use of oral contraception after the end of the study to one month based on pasireotide s.c half-life of approximately 12 hours, the amendment has reduced the use of oral contraception after the end of the study from 3 months to 1 month.

As per recently issued 2012 ADA and EASD guidelines, the SOM program has added further guidelines on the hyperglycemia management and monitoring of blood glucose for all SOM studies. These new guidelines have been incorporated into this amendment.

The current version of the study ends on 31December 2013. Several participating countries have not received pasireotide approval. To continue to provide access to these countries, the protocol has been extended to 31December 2015.

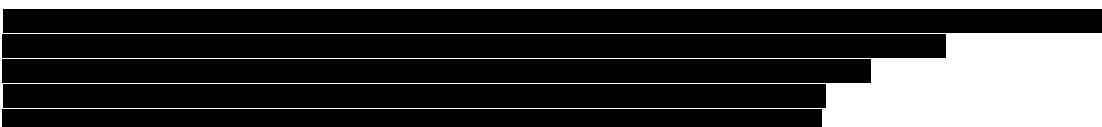
To be in compliance with the Expanded Access Program requirements, the amendment has added the new process of monthly AE reporting. Per SOM program's new guidance for AE reporting, the amendment has added events of special interest for pasireotide s.c. for targeted follow-up. Events of special interest should be notified to Novartis DS&E in the same manner as a SAE.

### Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol.

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

- Study duration is extended from 31December 2013 to 31December 2015 throughout the protocol
- 5.2 Inclusion criteria
  - The washout period for glucocorticoid receptor inhibitor (mifepristone) has been extended from 1 to 4 weeks before patients can be considered for screening
- 5.3 Exclusion criteria
  - The duration of oral contraception to be used after the end of the study has been reduced from 3 months to 1 month
  - 6.2.1.1 Follow-up for toxicities
    - This section was updated by removing the language for Glucose metabolism and adding the language for Hyperglycemia, Monitoring of blood glucose and adding Figure 6-1 for Fasting self-monitoring blood glucose (SMBG) guidelines
- 8.2.2 Reporting

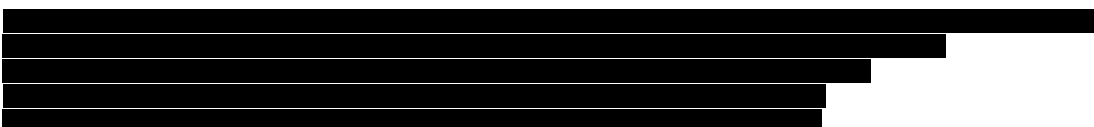


- This section was updated to introduce the language for all AE collection and updated in the study database on a periodic basis. Additionally, to add the events of special interest for pasireotide s.c. for targeted follow-up in the same manner as a SAE.

### **IRB/IEC/REB Approval**

A copy of this amended protocol must 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

### Amendment rationale

Based on the positive opinion and recommendation from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency on 19 January 2012, the starting dose of commercial pasireotide s.c for the treatment of Cushing's disease will be 600 µg b.i.d in all countries of the European Union with the option to increase the dose to 900 µg b.i.d. if the patient is not controlled (i.e. 24h-mean UFC levels above the upper limit of normal) at earliest after 2 months of treatment provided the 600 µg b.i.d dose is well tolerated by the patient. This protocol was adapted accordingly in order to be consistent with the future label, i.e. all patients included in countries of the European Union will start treatment with pasireotide 600 µg b.i.d. However ongoing patients in the study at the time of approval of amendment 3 will continue on their current dose. This change is not applicable for countries outside of the European Union. The results of study SOM230B2305 support the initial dose of 900 µg b.i.d. Therefore, countries outside the European Union will continue to use 900 µg b.i.d. as the starting dose in this trial.

In order to facilitate bridging the timeframe between the end of this study and the approval and reimbursement of commercial pasireotide, the treatment duration of maximum 1 year per country has been extended to the latest expected approval date in all participating countries. Therefore all patients will remain in the study until pasireotide is approved for commercial use and reimbursed or until 31 December 2013, whichever comes first.

In order to ensure collection of all efficacy and safety data at the time of the last study drug administration, a study phase completion visit has been introduced on the day of the last study drug administration including all safety and efficacy assessments. A study completion visit will then be performed 28 days after the last study drug administration with a limited number of assessments.

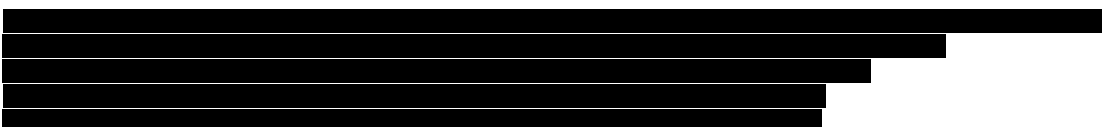
A timeframe for the transition from study drug to commercial pasireotide has been added in this amendment.

One secondary safety objective and corresponding endpoints have been added to be aligned with the Statistical section of the protocol.

A newly approved medication for the treatment of Cushing syndrome has been added in inclusion criterion 6 which lists previous medical treatments to be washed out before screening procedures are performed.

Preclinical data is available to show that pasireotide does not adversely affect the sperm. The fertility and early embryonic development study in the rat showed no effect on male reproductive parameters. Therefore the language describing the requirements for pregnancy outcomes for a female partner of any males who took study drug in this study has been removed. The protocol has been updated to allow for additional, country specific interim analysis in case of regulatory requirements.

The remaining changes/corrections were made to maintain consistency throughout the protocol and to correct minor editorial issues. As of the release date of this amendment,



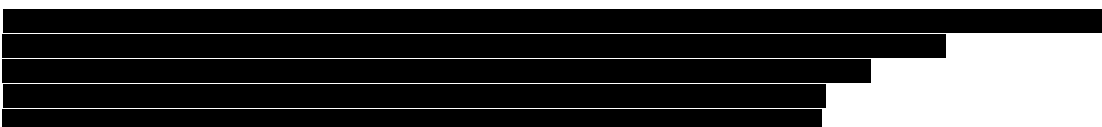
approximately 20 patients have been included in the study and are in the treatment phase. As a consequence of extension of study duration (see above), there is an impact of this amendment on the duration of recruitment and on the release of the results.

## Changes to the 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 sections affected are detailed below:

- Protocol Summary
  - Changes in the main body of the protocol (see bullet points below) are also implemented in the relevant sections of the protocol summary
- 2.3 Rationale for dose and regimen selection
  - Rationale for the 600 µg b.i.d starting dose in European Union has been added
- 3 Objectives and endpoints
  - As a consequence of extension of study duration, objectives and endpoints have been updated to include an additional timepoint for analysis at week 48
  - One secondary safety objective and corresponding endpoints have been added to be aligned with the Statistical section of the protocol
- 4.1 Description of study design
  - This section has been updated to reflect the change of the starting dose in the European Union and the change of study duration
- 4.2 Timing of interim analysis and design adaptations
  - This section has been updated to reflect the change of the study duration and to allow for selected efficacy and safety analyses to be repeated for subgroups of patients from specific countries
- 4.3 Definition of end of study
  - This section has been updated to reflect the change of the study duration
- 5.2 Inclusion criteria
  - A newly approved medication for the treatment of Cushing syndrome has been added in inclusion criterion 6
- 6.1.1 Dosing regimen
  - This section has been updated to reflect the change of the starting dose in the European Union
- 6.1.2 Treatment duration
  - This section has been updated to reflect the change of the study duration
- 6.3.1 Dose modifications
  - This section has been revised to describe the dose adjustments permitted for patients in the European Union starting with the 600 µg b.i.d dose
- 6.3.2 Treatment interruption and treatment discontinuation



- This section has been updated to introduce a study phase completion visit to be performed at the time of the last study drug administration and to provide a timeframe for the transition from study drug to commercial pasireotide
- Table 7-1 Visit evaluation schedule
  - This table has been updated to reflect the extension of the study duration and to introduce a study phase completion visit to be performed at the time of the last study drug administration as well as to reduce the number of assessments done at study completion visit.
- 7.1.2 Treatment period
  - This section has been updated to reflect the change of the study duration
- 7.1.3 Study phase completion visit, including premature withdrawal and study discontinuation visit
  - This section has been updated to introduce a study phase completion visit to be performed at the time of the last study drug administration
- 7.1.3.1 Criteria for premature patient withdrawal
  - Change of magnesium value from 0.7 mmol/L to 0.5 mmol/L since a magnesium value of 0.5 mmol/L does not have a significant negative effect on the cardiac status i.e., any magnesium value greater than 0.5 mmol/L is considered in the normal range.
- 8.4 Pregnancies
  - Removal of the language describing the requirements for pregnancy outcomes for a female partner of any males who took study drug in this study.
- 10 Statistical methods and data analysis
  - This section has been updated to reflect the change of the study duration
- 10.5.1.1, 10.5.1.2, 10.5.1.3, 10.5.1.4
  - As a consequence of extending the study duration, those sections have been revised to include an additional timepoint for analysis at week 48
- [REDACTED]
- [REDACTED]
- 10.7 Interim analysis
  - This section has been updated to reflect the change of the study duration and to allow for selected efficacy and safety analyses to be repeated for subgroups of patients from specific countries

The remaining changes/corrections were made to maintain consistency throughout the protocol and to correct minor editorial issues.

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.

[REDACTED]

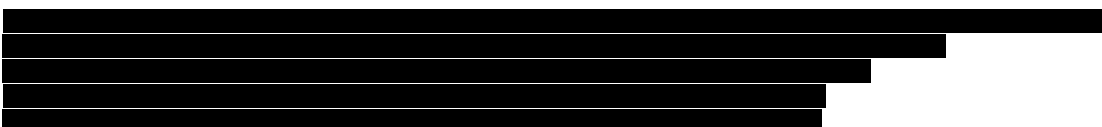
## Amendment 2

### Amendment rationale

This protocol is being amended to include additional hepatic-related safety measures as a result of an internal hepatic medical review of pasireotide trials. During this internal medical review of liver related laboratory values, 3 healthy volunteers were identified with elevations in liver function tests. Three subjects met the criteria for Hy's Law (i.e. ALT > 3 x ULN with concurrent total bilirubin >2 x ULN, without increases in alkaline phosphatase (ALP) and no other cause(s) identified for the abnormal findings). One subject received pasireotide 600 µg bid s.c. for 7 days, while the second subject received pasireotide 1950 µg bid s.c. for 5 days. The third subject (pasireotide 600 µg bid s.c. for 7 days) had ALT and total bilirubin increases that met the criteria for Hy's Law but the alkaline phosphatase was not assessed and the subject received a potentially confounding concomitant medication. ALT values for all 3 subjects were greater than 3 x ULN but < 4 x ULN and total bilirubin values were ≤ 4 x ULN. All 3 cases were asymptomatic, presented within 10 days after initial pasireotide s.c. administration, and were reversible with discontinuation of pasireotide. None of the cases were reported as adverse events and the subjects completed the respective studies per protocol.

An assessment of liver enzyme categorical outliers has been completed across the pasireotide s.c. development program (up to October 2011). The 3 healthy volunteers that met Hy's Law criteria (including the subject without the ALP value) are included amongst the 654 healthy volunteers as presented below. None of the other patients (i.e. Cushing's disease, carcinoid syndrome or acromegaly) in the development program met the criteria for Hy's Law.

- 654 healthy volunteers have been exposed to pasireotide s.c.:
  - 3 out of 654 (0.5%) met the biochemical criteria of Hy's Law
  - 16 out of 654 (2.4%) subjects had an ALT or AST > 3x ULN
  - 3 out of 654 (0.5%) of the healthy volunteers had an ALT or AST > 5xULN
  - 17 out of 654 (2.6%) subjects had a total bilirubin of 2xULN (including 7 patients with pre-existing liver disease and elevations of total bilirubin)
- 156 patients in phase 1 and phase 2 trials have been exposed to pasireotide s.c.:
  - None of the patients met the biochemical criteria of Hy's Law
  - 6 out of 156 (3.8%) patients had an ALT or AST > 3xULN
  - 4 out of 156 (2.6%) patients had an ALT or AST > 5xULN
  - 2 out of 156 (1.3%) patients had a total bilirubin of ≥ 2xULN;
- 162 patients with Cushing's disease in phase 3 trials have been exposed to pasireotide (s.c.):
  - None of the patients met the biochemical criteria of Hy's Law
  - 8 out of 162 (4.9%) patients had an ALT or AST > 3x ULN
  - 1 out of 162 (0.6%) patients had an ALT or AST > 5x ULN



- None of the patients out of 162 with Cushing's disease had a total bilirubin of  $\geq$  2xULN

The pasireotide Compassionate Use Program (approximately 200 patients as of October 2011) was also reviewed. A single Cushing's disease patient (PHHO2010AU13717) who was previously presented in an Investigator Notification in September 2010 was the only patient identified as meeting Hy's Law criteria.

A review of the unblinded data from the clinical program with the pasireotide long acting release (LAR) formulation did not reveal cases meeting the Hy's law criteria.

As a consequence of these observations, enhanced hepatic-related safety measures will be taken to ensure patient safety.

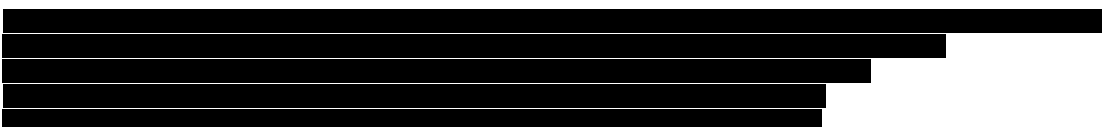
As of the release date of this amendment, approximately 5 patients have been included in the study and are in the treatment phase. There is no anticipated impact of this amendment on the duration of recruitment or on the release of the results.

### **Changes to the 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 major changes to the protocol and the sections affected are detailed below:

- Protocol Summary
  - Update of key exclusion criteria section reflecting new exclusion criteria 8, 17 and 18 of Section 5.3
- 5.3 Exclusion criteria
  - Exclusion criteria 11 and 12 have been revised
  - Exclusion criteria 17 and 18 have been added
  - Exclusion criterion 8 has been replaced by a more detailed exclusion criterion which still covers the former information of exclusion criterion 8.
- 6.3.1.1 Follow-up for toxicities
  - This section has been revised to describe the measures to be followed if the abnormal liver function criteria are observed.
  - Figure 6-2 has been added and describes the liver function test management algorithm
- Table 6-1 Guideline for treatment of patients experiencing adverse events
  - Clarification that detailed guidance in Section 6.3.1.1 has to be followed for hepatic safety management
- 7.1 Study flow and visit schedule
  - Figure 7-1 has been revised to reflect the additional LFT, PT/INR and serology assessments to be performed at screening and during the study
- 7.1.3.1 Criteria for premature patient withdrawal
  - Hepatic-related discontinuation criteria have been added
- 7.2.2.4.3 Clinical chemistry

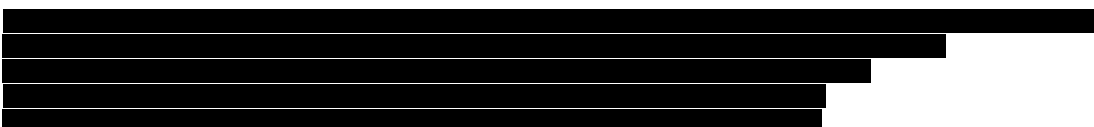


- This section has been revised. A sub-section “Liver function tests (LFT)” has been added and lists all parameters included in the LFT panel.
- 7.2.2.4.6 Serology
  - This section has been added to reflect the new serology assessments to be performed at screening.

### **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 in this amended protocol include the measures which have already been implemented as part of the Urgent Safety Communication, however still require submission to the IRB/IEC and approval.

In addition, as 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 1**

### **Amendment rationale**

In order to ensure a better standardization and quality of the laboratory results, it has been decided to use a central laboratory for the assessment of all parameters (except urinalysis) instead of local ones.

As of the release date of this amendment, no patient has been screened to the study. There is no anticipated impact of this amendment on the duration of recruitment or on the release of results.

### **Changes to the 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 changes to the protocol and the sections affected are detailed below:

- Removal of the sentences stating that laboratory parameters will be assessed by local laboratories in
  - Section 7.2.2.4 Laboratory evaluations and
  - Section 10.5.2.3 Laboratory abnormalities.

### **IRB/IEC/REB Approval**

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.



## 1 Background

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

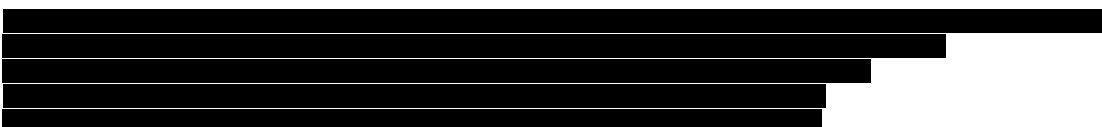
Cushing's disease (CD) is a devastating endocrine disease that is caused by an adrenocorticotrophic hormone (ACTH) secreting pituitary adenoma. Epidemiological studies indicated an annual incidence of 0.7-2.4 per million population ([Lindholm et al 2001](#)). However, a recent study performed in Belgium reported a much higher prevalence of CD ([Daly et al 2006](#)): 55 per million population. Eighty percent of these tumors can be classified as microadenomas, and 20% as macroadenomas. The elevated ACTH levels secreted by these tumors stimulate the adrenal glands to produce excess cortisol, leading to the subsequent development of the clinical signs and symptoms of hypercortisolism. Cushing's disease is rare, associated with severe morbidity and premature mortality and most commonly affects adults aged 20-50, primarily 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 due to excessive ACTH secretion. The primary clinical symptoms of Cushing's disease are due to hypercortisolism, and include the following:

- Change in body habitus: moon facies, supraclavicular fat pad, buffalo hump
- Hirsutism on face, neck, chest, abdomen, thighs
- Skin changes with easy bruising, purplish striae, reddening of the cheeks due to weakened connective tissue
- Generalized weakness and fatigue
- Wasting of musculature, particularly proximal muscles
- Menstrual disorders in females
- Decreased fertility and/or libido
- Hypertension
- Weight gain
- Diabetes mellitus
- Depression, mood and behavior disorders
- Sleep disturbances
- Osteopenia/osteoporosis

Most patients also develop a high set-point for feedback inhibition of ACTH secretion by cortisol.

In addition to the patient's medical history and physical examination, several laboratory test and diagnostic techniques are available for the diagnosis of Cushing's disease. Twenty four hour urinary free cortisol (UFC) measurements, blood sampling for serum cortisol levels, and the low-dose dexamethasone suppression test (LDDST) are widely used as screening tests for the diagnosis of Cushing's disease ([Newell-Price et al 1998](#)). To distinguish Cushing's





disease from other forms of hypercortisolism, a confirmation of a pituitary source of ACTH secretion is needed. This includes an inappropriately normal or elevated plasma ACTH level and evidence of pituitary tumor on magnetic resonance imaging (MRI) scan or confirmed by bilateral inferior petrosal sinus sampling (BIPSS) after corticotrophin-releasing hormone (CRH) stimulation test (evidence of a pituitary source of ACTH). It is generally accepted that if the ratio of adrenocorticotrophin concentration in the inferior petrosal sinuses to peripheral-blood is greater than or equal to 3.0 after CRH stimulation, a diagnosis of Cushing's disease can be made ([Oldfield et al 1991](#)).

The incidence of Cushing's disease ranges from 1-3 patients per million per year.

Pituitary resection of the adenoma is the current first-line therapy for Cushing's disease, but surgical failure rates are as high as 25-30% even in the hands of the most experienced neurosurgeons. Additionally postoperative recurrence rates are as high as 20% by 5 years ([Bochicchio 1995](#), [Sonino 1996](#)). Surgery is in many cases complicated by hypopituitarism, which requires complicated life-long hormonal replacement therapy necessary to sustain life. Treatment usually focuses on replacing the target hormones rather than the pituitary hormones, and in patients who have multiple axis deficiencies maintenance with multiple replacement hormones can be difficult, and requiring close and constant medical monitoring, and can be expensive ([Swearingen et al 1999](#)).

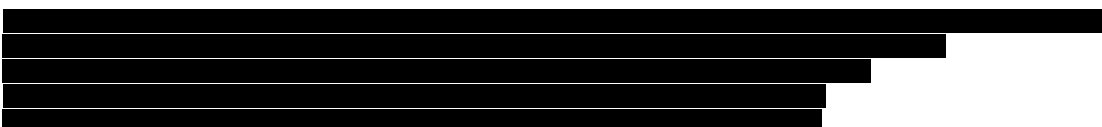
Irradiation of the pituitary is another option but it may take many years to be effective and it is curative in only 15 to 45% of the cases. In addition, due to its lack of specificity the procedure also often results in panhypopituitarism. Furthermore, there is a 1 to 2% risk of development of secondary tumors in the field of radiation over subsequent years ([Orth 1995](#)).

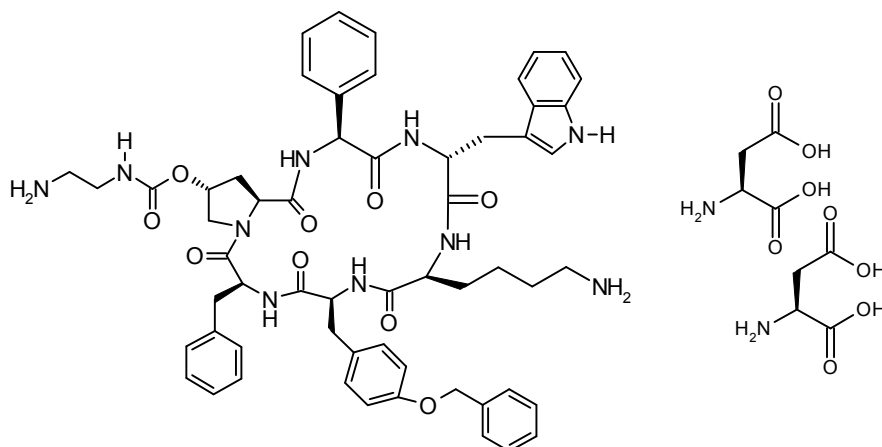
When surgery and/or irradiation fail, or for those patients for whom such therapies are not an option, the remaining alternative is pharmacological treatment. No drug is currently approved for the treatment of Cushing's disease and the ones which physicians are using are fraught with suboptimal results and significant side effects ([Miller 1993](#), [Nieman 2002](#)) preventing their long term use required in the management of CD. Therefore, a safe and effective targeted medical therapy is highly desirable in this patient population.

## **1.2 Introduction to investigational treatment**

### **1.2.1 Overview of Pasireotide**

Pasireotide 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 Pasireotide structural and molecular formulae**

Pasireotide free base on anhydrous basis:  $C_{58}H_{66}N_{10}O_9$

di-aspartate salt form on anhydrous basis:  $C_{58}H_{66}N_{10}O_9 \cdot 2 C_4H_7NO_4$

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 ([Schmid and Schoeffter 2004](#)) 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 ([Obergh 2004](#)) and Cushing's disease ([van der Hoek et al 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 et al 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 (Boscaro et al 2009).

Data from the recently completed [SOM230B2305] study showed the efficacy of pasireotide in reducing UFC in patients with Cushing's disease. In this randomized, double-blind, Phase III study, 162 adult patients with Cushing's disease and UFC >1.5x the upper limit of normal (ULN) were randomly allocated to received pasireotide 600 µg (n=82) or 900 µg (n=80) s.c. bid for 12 months. At the end of the study, patients entered an open-end extension study. Patients with UFC ≤2xULN and ≤baseline at month 3 continued on their randomized dose until month 6. All other patients received a dose increase of 300µg bid. At month 6, 14.6% (600µg) and 26.3% (900µg) of patients met the primary endpoint (i.e. patients with UFC≤ULN at month 6 without up-titration). Mean UFC decreased by approximately 50% in both groups of patients within 2 months and remained stable throughout the study. Patients with baseline UFC ≤5xULN were more likely to achieve normal UFC. Serum and salivary cortisol and plasma ACTH had a similar decrease, and clinical signs and symptoms of Cushing's disease improved as UFC decreased. The safety profile of pasireotide was similar to that of other somatostatin analogues (mostly transient GI discomfort), except for the degree of hyperglycemia.

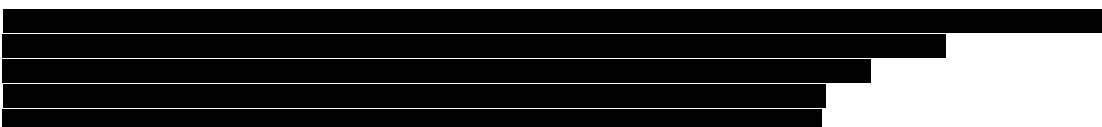
The [SOM230B2305] study showed a rapid and sustained UFC reduction in the majority of patients: achieving normalization in a subset of them. In addition, clinical benefit was observed irrespective of achieving normal UFC. Pasireotide is a pituitary-directed medical treatment that has shown benefits to patients with CD.

Pasireotide has also shown activity in the treatment of acromegalic and carcinoid tumor patients inadequately controlled by other somatostatin analogs. Pasireotide appears to be well tolerated at doses up 600 µg b.i.d. and 1200 µg b.i.d. by acromegalic and carcinoid tumors patients respectively.

### 1.2.2 Known undesirable effects of Pasireotide

In healthy volunteers the adverse events most frequently reported during pasireotide treatment are gastrointestinal, most commonly being diarrhea and loose stools. Mild nausea and vomiting have also been reported. Generally these events do not require treatment and event frequency and severity appears to decrease with continued exposure to pasireotide.

Pasireotide administration may transiently increase fasting and/or post-prandial blood glucose levels. In a mechanistic study in healthy volunteers [SOM230B2216], pasireotide at doses of 600 and 900 µg b.i.d. decreased the hyperglycemia-induced and arginine-maximal-stimulated insulin secretion (AIR max.) with no changes in peripheral or hepatic insulin sensitivity. Pasireotide s.c. was also associated with a significantly decreased insulin-incretin response (i.e., GLP-1 and GIP levels) following an OGTT. These elevations are commonly transient, showing a clear attenuation of effect with subsequent exposure to pasireotide. Glucagon secretion is also suppressed. These finding are similar to those observed with other somatostatin analogues.



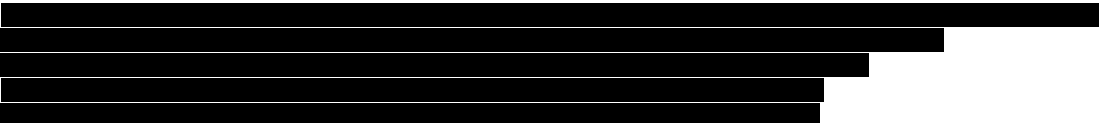
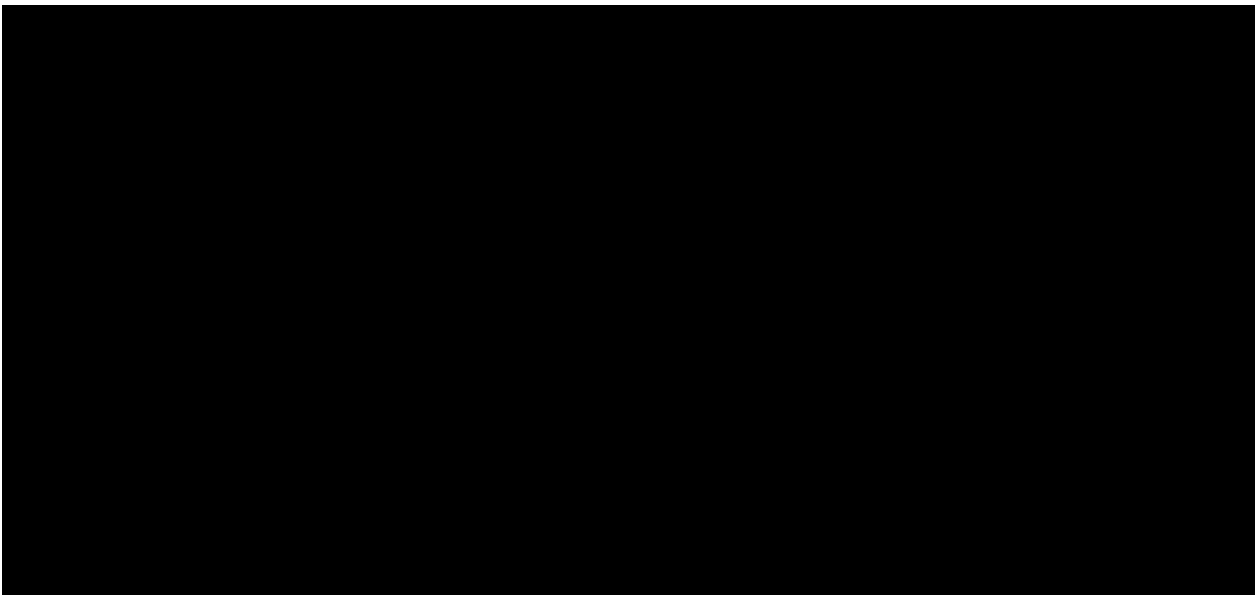
Increases in blood glucose in patients with Cushing's disease were observed during the Phase II study. Blood glucose increases tended to occur with increasing dose, and were most prominent in patients with a history of hyperglycemia or diabetes mellitus. In general however, when needed, the increases were managed by adjustment or addition of hypoglycemic medications.

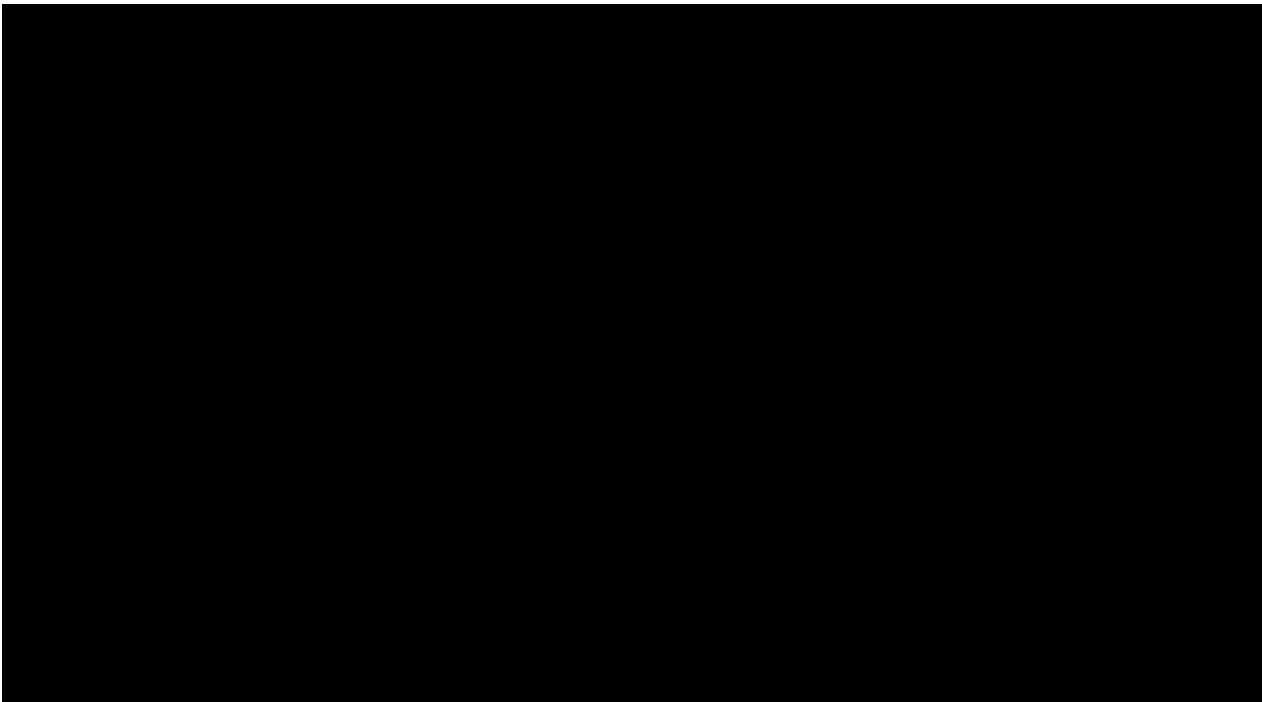
Laboratory abnormalities in liver function tests and pancreatic enzymes have been observed at higher doses in some subjects receiving the continuous infusion of pasireotide administered subcutaneously via an insulin pump. These events, however, have all been transient and asymptomatic at doses as high as 2250 µg s.c.

Furthermore, results from the thorough QT/QTc (TQT) study [CSOM230B2113] provided data on the QT/QTc intervals of a supra-therapeutic dose of pasireotide in healthy volunteers. The study was divided in two parts. In part 1, a maximum tolerated dose (MTD) of 1950 µg b.i.d. was identified. In part 2, the effects of pasireotide at MTD on the cardiac intervals were investigated. Pasireotide showed a peak effect on QTcF at 2 hours post-dose. There was a +10.0ms increase from baseline that correlates to a 17.5 msec difference versus placebo, while placebo had a -7.4 msec decrease from the baseline 2 hour post-dose. A similar effect was demonstrated on QTcI, but not observed on QTcB interval. Pasireotide subjects also showed a reduction of the heart rate at 0 to 4 hours post-dose with the maximum change versus baseline of 10.7 bpm.

A second thorough QT study [CSOM230B2125] is ongoing to further investigate the effect of pasireotide on QT/QTc intervals.

Study [CSOM230B2305] has shown that the safety profile of pasireotide is similar to other somatostatin analogues with the exception of hyperglycemia. As expected with effective treatment for Cushing's disease, some patients [13/162 (8%) randomized patients] experienced symptoms of hypocortisolism. No deaths were observed during pasireotide treatment, and the most frequently reported AEs included gastrointestinal AEs similar to approved somatostatin analogues: diarrhea (54.9 %), nausea (46.9%), cholelithiasis (29.6%), abdominal pain (20.4%). 70% of patients had at least one hyperglycemia-related AE.





## **2 Rationale**

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

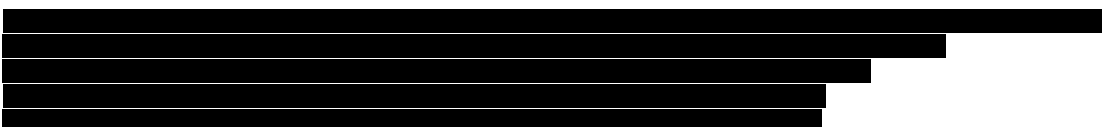
The trial is planned as an Expanded Access study to provide access and to further document the safety and the efficacy of pasireotide in patients affected by Cushing's disease. While regulatory approval is sought, there are no means available for patients with Cushing's disease to receive pasireotide outside of a clinical trial. Patients with post-surgery active disease or patients who recur after surgery and de novo patients that are not candidates to surgery do not have an access path to this new agent. Implementation of an Expanded Access Program will allow access to pasireotide for patients with Cushing's disease.

### **2.2 Rationale for study design**

The rationale for this study is to give patients with Cushing's disease access to pasireotide s.c. as no medical treatment for Cushing's disease is approved. Thus, a single arm, open label design is justified in this context

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

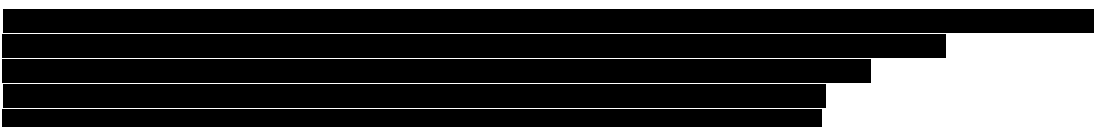
Results from the pivotal study [SOM230B2305] showed that the 900 µg b.i.d dose met the primary endpoint and can be used as a starting dose. In addition, it was observed that patients with impaired glucose metabolism had a less pronounced increase in blood glucose when using the 600 µg b.i.d dosing. [Applicable for countries outside the European Union] Therefore, this study will use the 900 µg b.i.d as starting dose in all patients except the ones affected by impaired glucose metabolism that will have the 600 µg b.i.d as starting dose



[Applicable for countries in the European Union] Based on the positive opinion and recommendation from CHMP on 19 January 2012, the starting dose of commercial pasireotide s.c for the treatment of Cushing's disease will be 600 µg b.i.d for all patients coming from European Union countries. Accordingly, the starting dose in this study will be 600 µg b.i.d in all patients (including the ones affected by impaired glucose metabolism) with the option to increase the dose to 900 µg b.i.d. if the patient is not controlled (i.e. 24h-mean UFC levels above the upper limit of normal) at earliest after 2 months of treatment provided the 600 µg b.i.d dose is well tolerated by the patient. However patients on going in the study at the time of approval of amendment 3 will continue on their current dose.

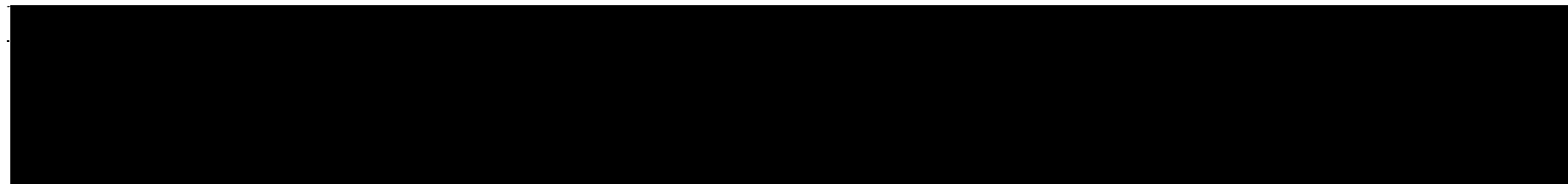
### **3 Objectives and endpoints**

Objectives and related endpoints are described in [Table 3-1](#) below.



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

Objective	Endpoint	Analysis
<b>Primary</b>		
To document the safety of pasireotide s.c. in patients with CD	The proportion of patients having a drug-related adverse event that is recorded as grade 3 or 4 or as a serious adverse event.	Refer to <a href="#">Section 10.4</a> .
<b>Secondary</b>		
To document the efficacy of pasireotide s.c. in normalizing mean 24h-UFC at Week 12, 24 and 48, separately	The proportion of patients with mean 24h-UFC $\leq$ ULN at Week 12, 24 and 48, separately	Refer to <a href="#">Section 10.5.1</a> .
To document the efficacy of pasireotide s.c. in achieving at least 50% reduction of mean 24h-UFC from baseline at Week 12, 24 and 48, separately	The proportion of patients achieving a reduction of mean 24h-UFC $\geq$ 50% from baseline at Week 12, 24 and 48, separately	
To document the changes in clinical signs and symptoms	The change from baseline to Week 12, 24 and 48 in clinical signs and symptoms	
To document the changes in patient-reported outcome questionnaires (CushingQoL and WPAI-GH)	The change from baseline to Week 12, 24 and 48 in CushingQoL and WPAI-GH scores	
To document the effects of pasireotide s.c. on the GH/IGF-I axis	The change from baseline to Week 12, 24 and 48 in GH and IGF-I separately	
To document the overall safety and tolerability of pasireotide s.c. in patients with CD	Incidence of AEs, and laboratory, vital signs and electrocardiographic abnormalities. Changes in laboratory values, electrocardiograms readings, and in vital signs values.	



## 4 Study design

### 4.1 Description of study design

This is an open-label, uncontrolled, single-arm, multi-center, multi-national expanded access study. The starting dose will be:

- [Applicable for countries in the European Union] 600 µg b.i.d. (twice daily) in all patients also including the ones with impaired glucose metabolism with the option to increase the dose to 900 µg b.i.d. if the patient is not controlled (i.e. 24h-mean UFC levels above the upper limit of normal) at earliest after 2 months of treatment provided the 600 µg b.i.d dose is well tolerated by the patient. However ongoing patients in the study at the time of approval of amendment 3 will continue on their current dose.
- [Applicable for countries outside the European Union] 900 µg b.i.d. (twice daily). The initial dose for patients with impaired glucose metabolism will be 600 µg b.i.d

Refer to [Section 6.2.1](#) for allowed dose modifications.

After a 21-day screening period, patients who satisfy all the inclusion/exclusion criteria will start receiving pasireotide s.c. twice a day. Please, refer to [Table 7-1](#) for a description of the screening evaluations required. During the first 24-week period, patients will have a visit on a weekly basis up to week 4 and will then be followed on a 4-week basis up to week 24. In the second study period, patients will be followed at 12-week intervals until the end of the study. Patients will be treated until the drug is approved for commercial use and reimbursed in each respective country or until 31 December 2015 (until 31 December 2016 for sites in South Korea and Brazil), whichever occurs first.

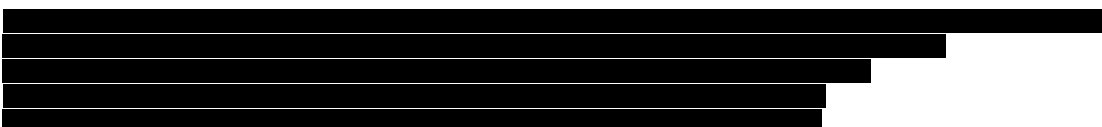
### 4.2 Timing of interim analyses and design adaptations

No formal interim analysis is planned. However, since the timing of drug approval may differ between regions, data from a specific region may be reported when all patients from that region have been followed for 28 days after they have either prematurely discontinued pasireotide s.c. or after completing treatment as per protocol (i.e. when the study drug is approved for commercial use and reimbursed in each respective country or until 31 December 2015 (until 31 December 2016 for sites in South Korea and Brazil), whichever occurs first). For regulatory purposes, at time of a regional interim analysis, data from countries where the trial is still ongoing may be included. Furthermore, independent of a regional interim analysis additional interim analysis may be performed for regulatory or publication purpose.

No design adaptations are planned.

### 4.3 Definition of end of the study

Patients will be treated until the drug is approved for commercial use and reimbursed in each respective country or until 31 December 2015 (until 31 December 2016 for sites in South Korea and Brazil), whichever occurs first. Should pasireotide not be approved for commercial use and reimbursed 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. End of the study will thus be reached once LPLV (28 days after the last dose) in the last participating country has occurred.

#### 4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in [Table 7-1](#) for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

## 5 Population

### 5.1 Patient population

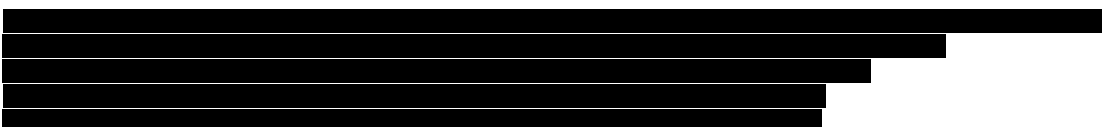
The study population will consist of patients with persistent or recurrent Cushing's disease or patients with de novo Cushing's disease that are not considered candidates for pituitary surgery (poor surgery candidates, surgically unapproachable tumor, patients with no visible pituitary tumor, patients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

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered enrollment in the study.

### 5.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

1. Written informed consent obtained prior to any screening procedures
2. Male or female patients aged 18 years or greater
3. Patients with confirmed diagnosis of Cushing's disease as evidenced by
  - mean urinary free cortisol of three 24-hour urine samples collected during the 3-week screening period above the upper limit of the laboratory normal range
  - morning plasma ACTH within the normal or above normal range
  - either MRI confirmation of pituitary adenoma (greater than or equal to 0.6 cm), or inferior petrosal sinus gradient >3 after CRH stimulation for those patients with a microadenoma less than 0.6 cm\*, or for patients who have had prior pituitary surgery, histopathology confirming an ACTH staining adenoma. (\* 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)
4. Patients with de novo Cushing's disease must not be considered as candidates for pituitary surgery (i.e. poor surgical candidates, surgically unapproachable tumors, patients with no visible pituitary tumor, patients who refuse to have surgical treatment)
5. Karnofsky performance status >60 (i.e. requires occasional assistance, but is able to care for most of his personal needs)



6. For patients on previous medical treatment for Cushing's disease the following washout periods must be completed before screening assessments are performed
  - Inhibitors of steroidogenesis (e.g. ketoconazole, metyrapone, rosiglitazone): 1 week
  - Dopamine agonists (e.g. bromocriptine, cabergoline): 4 weeks
  - Mitotane: 6 months
  - Octreotide LAR and Lanreotide autogel: 8 weeks
  - Lanreotide SR: 4 weeks
  - Octreotide (immediate release formulation): 1 week
  - Glucocorticoid receptor inhibitor (mifepristone): 4 weeks

### 5.3 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. Radiotherapy of the pituitary <4 weeks before screening or patient who has not recovered from side effects
2. Patients with compression of the optic chiasm causing acute clinically significant visual field defect
3. Patients with Cushing's syndrome due to ectopic ACTH secretion
4. Patients with hypercortisolism secondary to adrenal tumors or nodular (primary) bilateral adrenal hyperplasia
5. Patients who have a known inherited syndrome as the cause for hormone over secretion (i.e. Carney Complex, McCune-Albright syndrome, MEN-1)
6. Patients with a diagnosis of glucocorticoid-remedial aldosteronism (GRA)
7. Patients who have undergone major surgery within 1 month prior to screening
8. Patients with known gallbladder or bile duct disease, acute or chronic pancreatitis (patients with asymptomatic cholelithiasis and asymptomatic bile duct dilation can be included)
9. Diabetic patients whose blood glucose is poorly controlled as evidenced by HbA<sub>1C</sub> >8%
10. Patients who have clinically significant impairment in cardiovascular function or are at risk thereof, as evidenced by
  - congestive heart failure (NYHA Class III or IV), unstable angina, sustained ventricular tachycardia, clinically significant bradycardia, high grade AV block, history of acute MI less than one year prior to study entry
  - QTcF >450 msec at screening
  - History of syncope or family history of idiopathic sudden death
  - Risk factors for Torsades de Pointes such as uncorrected hypokalemia, uncorrected hypomagnesemia, cardiac failure
  - Concomitant disease(s) that could prolong the QT interval such as autonomic neuropathy (caused by diabetes or Parkinson's disease), HIV, cirrhosis, uncontrolled hypothyroidism, concomitant medication(s) with known risk for TdP
11. Patients with liver disease or history of liver disease such as cirrhosis, chronic active hepatitis B and C, or chronic persistent hepatitis, or patients with ALT or AST more than



- 2 x ULN, serum creatinine >2.0 x ULN, serum bilirubin >1.5 x ULN, serum albumin < 0.67 x LLN at screening
12. Patients who have any current or prior medical condition that can interfere with the conduct of the study or the evaluation of its results, such as
    - History of immunocompromise, including a positive HIV test result (Elisa and Western blot). An HIV test will not be required, however, previous medical history will be reviewed
    - Presence of active or suspected acute or chronic uncontrolled infection
    - History of, or current alcohol misuse/abuse in the 12 month period prior to screening
  13. Female patients who are pregnant or lactating, or are of childbearing potential and not practicing a medically acceptable method of birth control. If a woman is participating in the trial then one form of contraception is sufficient (pill or diaphragm) and the partner should use a condom. If oral contraception is used in addition to condoms, the patient must have been practicing this method for at least two months prior to screening and must agree to continue the oral contraceptive throughout the course of the study and for one month after the study has ended. Male patients who are sexually active are required to use condoms during the study and for three month afterwards as a precautionary measure (available data do not suggest any increased reproductive risk with the study drugs)
  14. Patients who have participated in any clinical investigation with an investigational drug within 1 month prior to screening or patients who have previously been treated with pasireotide
  15. Known hypersensitivity to somatostatin analogues
  16. 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
  17. Patients with presence of Hepatitis B surface antigen (HbsAg)
  18. Patients with presence of Hepatitis C antibody test (anti-HCV)

## 6 Treatment

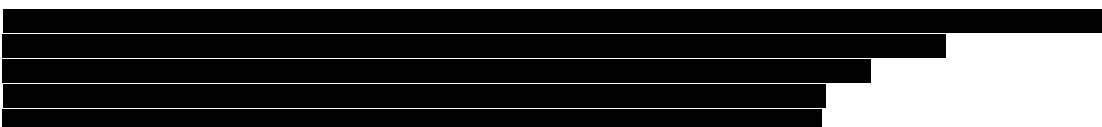
### 6.1 Investigational treatment, other treatment, supportive treatment

The investigational study drug used in the course of this trial is pasireotide for subcutaneous (s.c.) administration.

#### 6.1.1 Dosing regimen

The starting dose will be:

- [Applicable for countries in the European Union] 600 µg b.i.d. (twice daily) in all patients also including the ones with impaired glucose metabolism with the option to increase the dose to 900 µg b.i.d. if the patient is not controlled (i.e. 24h-mean UFC levels above the upper limit of normal) at earliest after 2 months of treatment provided the 600 µg b.i.d dose is well tolerated by the patient. However ongoing patients in the study at the time of approval of amendment 3 will continue on their current dose.



- [Applicable for countries outside the European Union] 900 µg b.i.d. (twice daily). The initial dose for patients with impaired glucose metabolism will be 600 µg b.i.d

### 6.1.2 Treatment duration

Patients will be treated until the drug is approved for commercial use and reimbursed in each respective country or until 31 December 2015 (until 31 December 2016 for sites in South Korea and Brazil), whichever occurs first. Should pasireotide not be approved for commercial use and reimbursed 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.

## 6.2 Dose escalation guidelines

[Applicable for countries in the European Union] Refer to corresponding paragraphs in [Section 6.2.1](#).

### 6.2.1 Dose modifications

**Uncontrolled disease** [Applicable for countries in the European Union]:

If the patient is not controlled with pasireotide 600 µg b.i.d (i.e. 24h-mean UFC levels above the upper limit of normal) after 2 months of treatment, the dose will be increased to 900 µg b.i.d provided the 600 µg b.i.d dose is well tolerated by the patient. Dose increase will be done as soon as UFC results from Visit 7 are available or at the latest at Visit 8.

In case the dose cannot be increased to 900 µg b.i.d after Visit 7 or at the latest at Visit 8 due to tolerability issues, the dose should be considered to be increased at subsequent visits provided 24h-mean UFC levels are still above the upper limit of normal and safety issues have been resolved.

If patients have been controlled with the 600 µg b.i.d dose but are no longer controlled (i.e. 24h-mean UFC levels above the upper limit of normal) with this dose at any time in the study after Visit 7, the dose will be increased to 900 µg b.i.d provided the 600 µg b.i.d dose is well tolerated by the patient. Dose increase will be done as soon as UFC results are available or at the latest at the next visit.

#### **Disease control:**

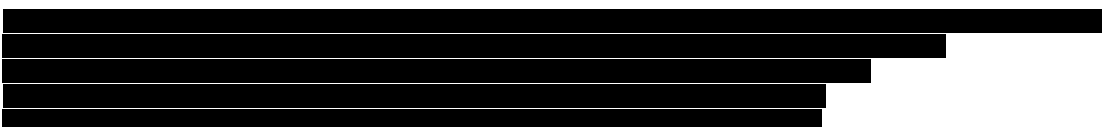
Patients having sustained mean 24h-UFC normalization evidenced by at least 2 consecutive normal 24h-mean UFC may have their pasireotide dose reduced, at the discretion of the investigator.

- Patients receiving 900 µg s.c. b.i.d., will be reduced to receive 600 µg s.c. b.i.d.
- Patients receiving 600 µg s.c. b.i.d., will be reduced to receive 300 µg s.c. b.i.d.

Should UFC levels increase above the upper limit of normal after down-titration, the dose should be up-titrated to the previous one.

#### **Safety issues:**

For patients who are unable to tolerate the protocol specified dose level, guidelines described in [Table 6-1](#) have to be followed.



At any time during the study, patients with an early morning (between 8 and 10 am) serum cortisol < 3 µg/dl and a mean 24h-UFC measurement < LLN or symptoms suggestive of hypoadrenalism (e.g. postural hypotension, nausea, and abdominal pain) in association with a mean 24h-UFC measurement < LLN should have their dose reduced by 300 µg b.i.d. Patients should return to their previous dose once the tolerability issue resolves.

Any dose changes must be recorded on the Dosage Administration Record.

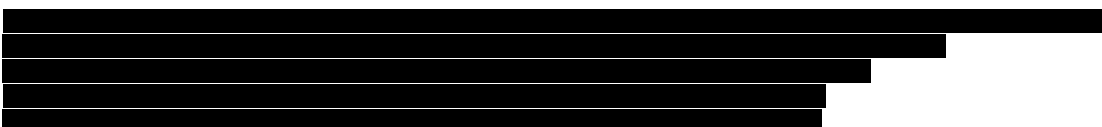
### 6.2.1.1 Follow-up for toxicities

#### Hyperglycemia

Hyperglycemia is known to be associated with the treatment of somatostatin analogues (SSA). 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.

#### Monitoring of blood glucose:

The principal investigator is to educate the patient on the signs and symptoms of hyperglycemia. In addition to the laboratory evaluation of blood glucose level at the regular scheduled visits (Table 7-1), patients are asked to self-monitor their blood glucose using a home glucometer provided by Novartis at least 3 times per week for the first month of pasireotide treatment. If the patient does NOT have any fasting values above 100mg/dL, monitoring can be decreased to at least 2 times per week for months 2 and 3 and 1 time every 2 weeks for months 4 through 7. If glucose levels remain normal (below 100mg/dL), monitoring is at the investigator's discretion after month 7. If any values are observed above 100 mg/dL, the guidelines in figure below 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 <130 mg/dL (<7.2 mmol/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 >130 mg/dL by self-monitoring), a fasting plasma glucose sample using the local laboratory is to be collected prior to initiation of anti-hyperglycemic treatment. If a patient has a dose increase, monitoring for hyperglycemia should follow the recommendations for the first month of treatment and continue as presented above for subsequent months.

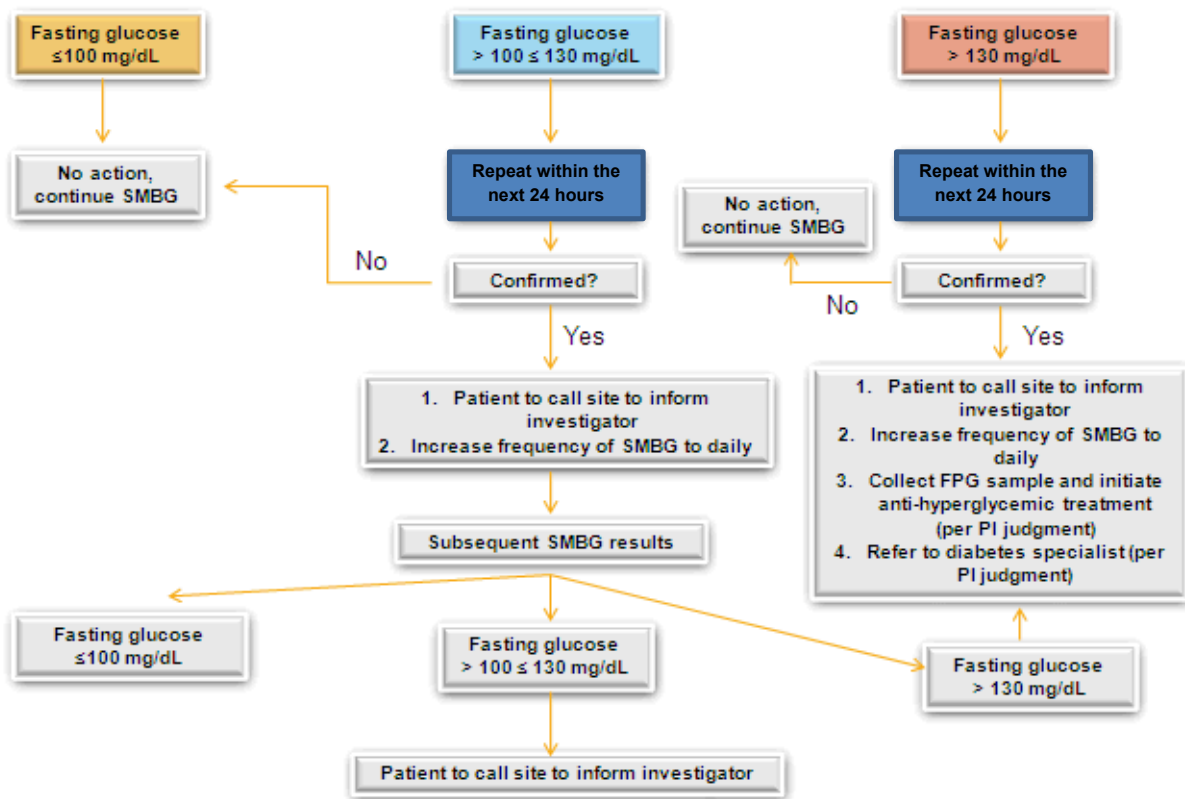


It is recommended that the patients be encouraged to keep a diary for their blood glucose for appropriate management throughout the study and present the collected data to their physician/diabetes specialist for evaluation. This data will not be collected by the sponsor.

In addition to self-monitoring, fasting plasma glucose and HbA1c will be collected at study visits per Table 7-1. 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 > 130 mg/dL or HbA1c ≥ 6.5 %.

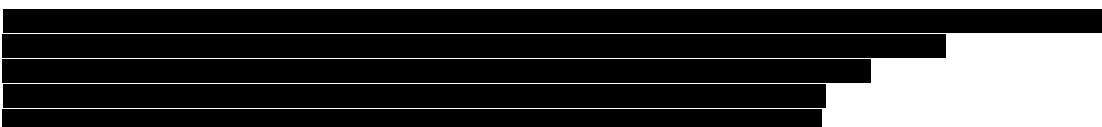
Patients with FPG > 160 mg/dL or HbA1c >7.5% despite adjustment of antidiabetic therapy should be referred to a diabetes specialist (or earlier per investigator’s judgment).

**Figure 6-1 Fasting self-monitoring blood glucose (SMBG) guidelines**



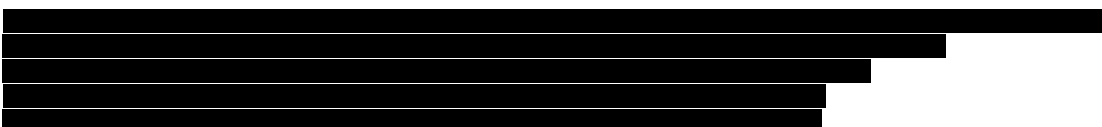
**QT prolongation:**

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 > 500 msec, 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 > 500 msec, the patient will be withdrawn from the study. Otherwise and if the cardiologist confirms that at least one ECG shows QTcF > 480 msec, the cardiac assessments described for a confirmed QTcF > 480 msec are to be followed.

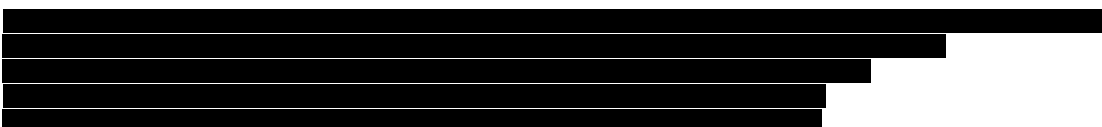
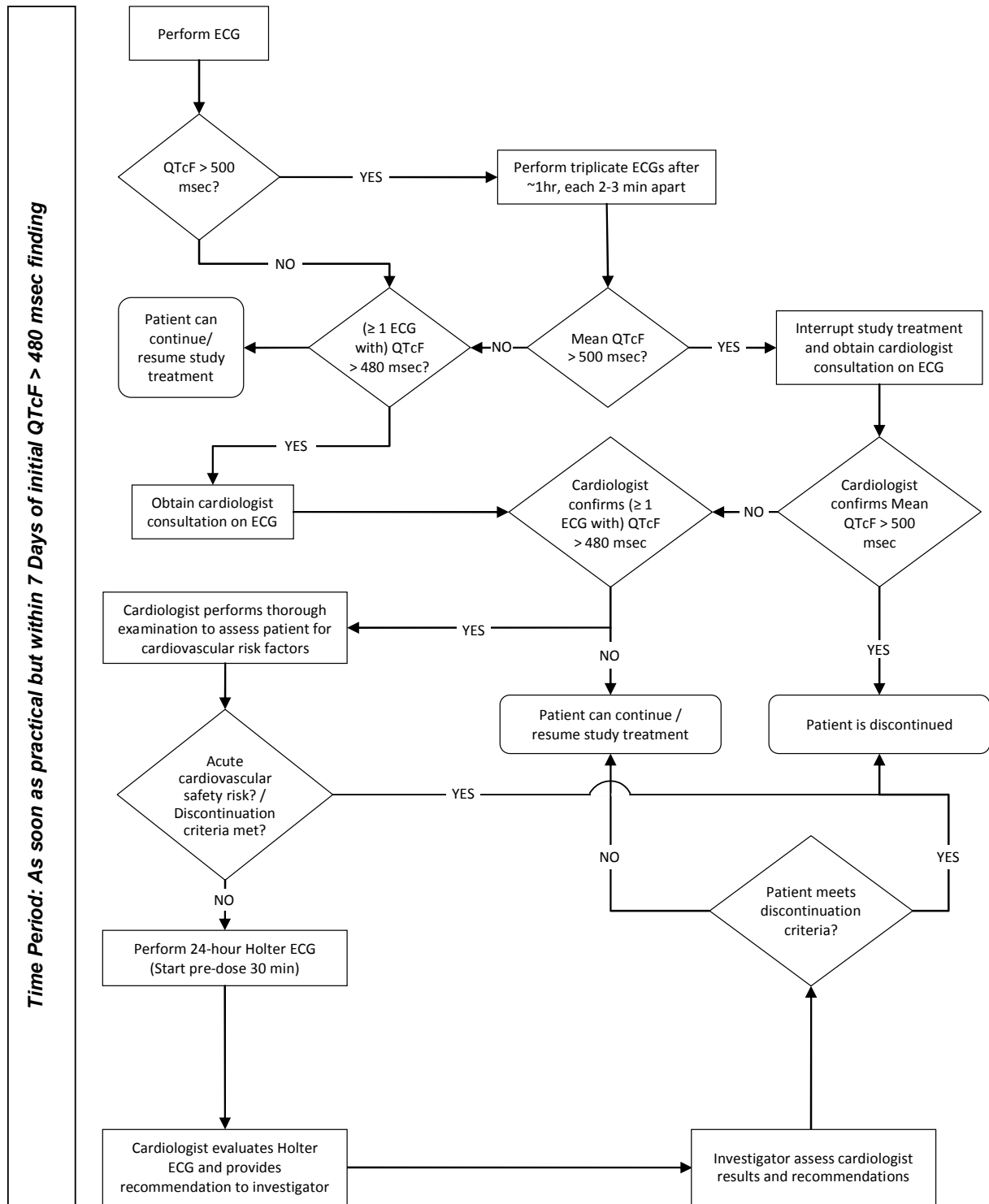


If at any visit a  $480\text{msec} < \text{QTcF} \leq 500\text{msec}$  is observed for the first time for a patient at a given dose level, the following steps are to be taken (as described in [Figure 6-2](#)):

- 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  $\text{QTcF} > 480\text{msec}$  is NOT confirmed, no further action is to be taken
  - If a  $\text{QTcF} > 480\text{msec}$  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 Holter-ECG 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**





### Hepatic safety management:

If any of the criteria below are observed at any scheduled or unscheduled visit the sponsor should be notified immediately upon awareness.

- ALT or AST > 3 x ULN and Total Bilirubin  $\geq$  2 x ULN
- ALT or AST > 5 x ULN and  $\leq$  8 x ULN
- ALT or AST > 8 x 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 chemistry tests: ALT, AST, total bilirubin, (fractionate to direct/indirect bilirubin if total bilirubin is > 2.0 x 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 chemistry tests (LFTs) should be monitored every **3-4 days** until resolution or return to baseline status.

Patients or subjects may need to be discontinued if the abnormal liver function criteria are met upon LFT retesting (See discontinuation criteria [Section 7.1.3.1](#)). Progress reports of the event should be maintained until resolution or stabilization (i.e. no further elevation after 2 consecutive assessments).

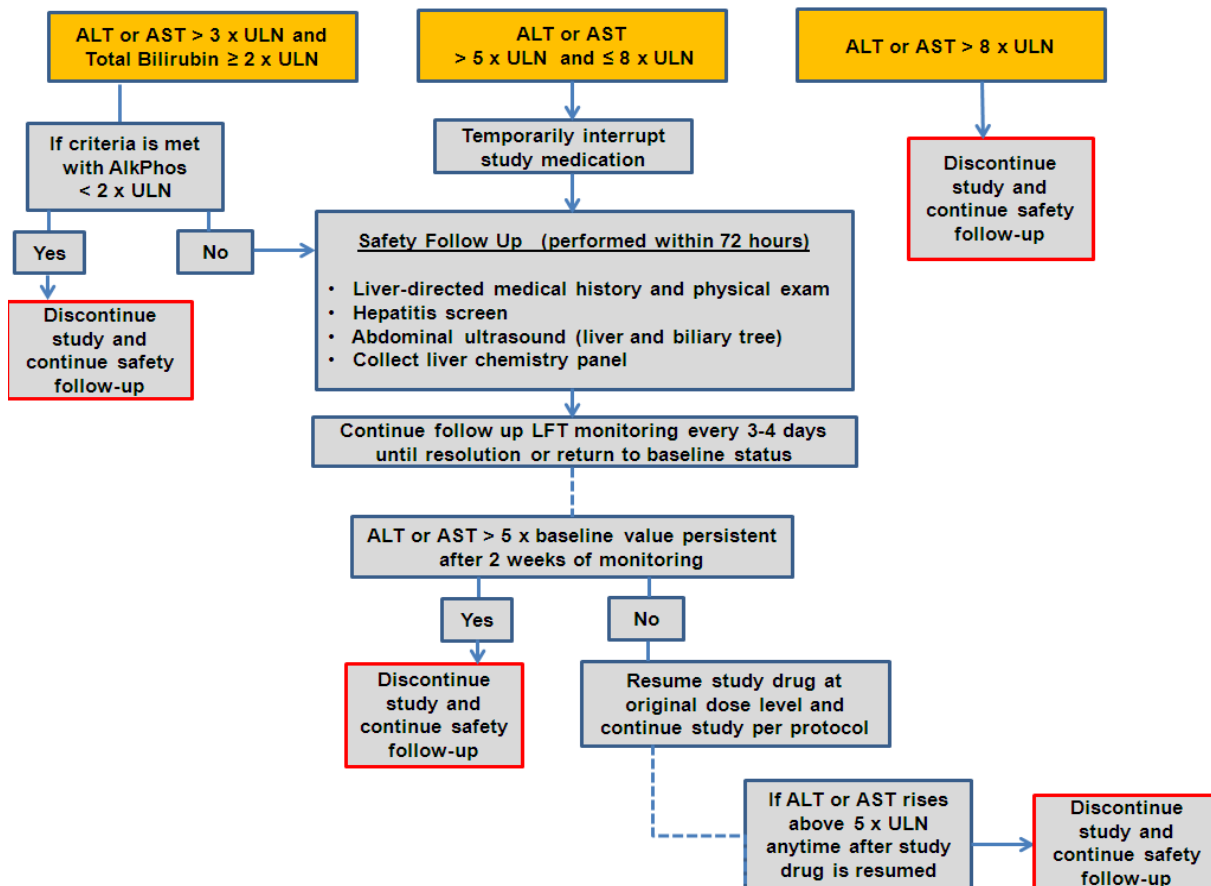
For ALT or AST > 5 x ULN and  $\leq$  8 x ULN, the following must occur (in addition to the safety follow up procedures noted above)

- Study medication should be temporarily interrupted and liver chemistry tests monitored every **3-4 days** until resolution or return to baseline.
- If resolution or return to baseline does not occur after 2 weeks, the patient should be discontinued.
- If ALT or AST return to less than 5 x ULN study drug can be resumed and patient can continue study per protocol.
- If ALT or AST rises above 5 x ULN anytime after study drug is resumed, then study drug should be discontinued immediately.

If any of these criteria are met and deemed an adverse event by the investigator, the event must be recorded on the Adverse Event (e) CRF 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 (e) CRF page.



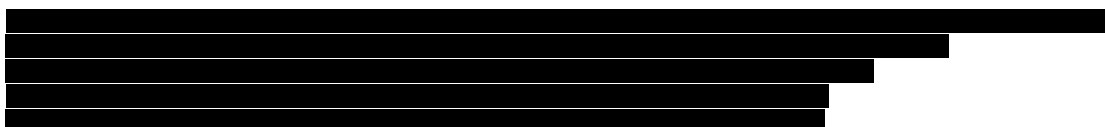
**Figure 6-3 LFT management algorithm**



### 6.2.2 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 6-1 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.

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 6-1).



**Table 6-1 Guideline for treatment of patients experiencing adverse events**

Patients	Adverse event	Action
All	AE grade $\leq$ 2 (mild to moderate) AE grade $\geq$ 3 (severe to life-threatening) and judged as drug related*#	No drug adjustments  Reduce dose by 300 $\mu$ g b.i.d. If AE improves to grade $\leq$ 2 within 1 week, increase dose by 300 $\mu$ g b.i.d. If AE recurs at grade $\geq$ 3, reduce dose by 300 $\mu$ g b.i.d. again and remain at lower dose. If AE does not improve to grade $\leq$ 2 within 1 week on lower dose, reduce dose by 300 $\mu$ g b.i.d. again if possible. If AE does not improve to grade $\leq$ 2 within 1 week on 300 $\mu$ g b.i.d., patient is to discontinue treatment.  For patients experiencing hyperglycemia, the dose should be reduced if the severity grade 3 or greater persists despite appropriate management.* If the hyperglycemia is considered to be life-threatening, the patient should be withdrawn regardless of anti-diabetes treatment.

\* CTCAE v3.0 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 of appropriate management.

# No dose reductions are required in case of a QT prolongation but guidelines for QT monitoring and discontinuation criteria must be observed.

Note: for hepatic safety management follow [Section 6.2.1.1](#).

If a patient permanently discontinues study treatment, the patients will be considered as prematurely discontinued from the study. Patients will have to perform a study phase completion evaluation on the day of the last study drug administration (refer to Study Phase Completion evaluation in [Table 7-1](#)).

Patients must be transitioned to commercial pasireotide within 6 weeks after approval and reimbursement in each respective country. Patients who complete the study because they are transitioned to commercial pasireotide are considered completed and will have to perform a study phase completion evaluation on the day of the last study drug administration (refer to Study Phase Completion evaluation in [Table 7-1](#)).

Patients who are treated until 31 December 2015 (until 31 December 2016 for sites in South Korea and Brazil) will be considered as completed patients. They will have to perform a study phase completion evaluation on the day of the last study drug administration (refer to Study Phase Completion evaluation in [Table 7-1](#)).

### 6.3 Concomitant medications

All medications, including over the counter medications (OTC), taken prior to the first study drug administration and which continue after visit 2 (beginning of the treatment) are to be recorded on the Concomitant Medication section of the CRF.

However, investigators should discourage patients from taking any medication during the study, with the exception of medications that are required to treat an adverse event.



### **6.3.1 Permitted concomitant therapy**

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. 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 by their physician/diabetes specialist.

### **6.3.2 Prohibited concomitant therapy**

Rosiglitazone and pioglitazone treatment are not permitted during the study as they could affect the patient's ACTH levels.

Further, the use of concomitant medications with known risk of TdP is prohibited and requires the discontinuation of the patient prior to starting the respective medication with known risk of TdP. The list of updated medications with known risk of TdP can be found at the following link: <http://crediblemeds.org/>

## **6.4 Patient numbering, treatment assignment and randomization**

### **6.4.1 Patient numbering**

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 No. 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.

### **6.4.2 Treatment assignment and randomization**

Randomization is not applicable in the study.

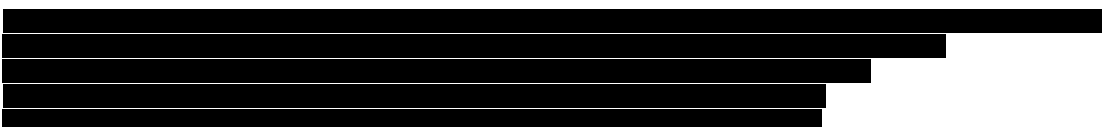
### **6.4.3 Treatment blinding**

This is an open-label study and blinding is not applicable.

## **6.5 Study drug supply**

### **6.5.1 Study drug preparation and dispensation**

Novartis will supply the investigational drug in 1 ml ampoules containing 900 µg, 600 µg, or 300 µg pasireotide per 1 ml of solution.



Patients must be able to self-administer the study drug (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 may not be re-used; a new ampoule should be used for each injection. Patients should be instructed to retain and return unused ampoules at their next scheduled visit.

All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

### **6.5.2 Study drug packaging and labeling**

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug but no information about the patient.

### **6.5.3 Drug supply and storage**

Study treatments must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Upon receipt, pasireotide should be stored according to the instructions specified on the drug labels.

### **6.5.4 Study drug compliance and accountability**

#### **6.5.4.1 Study drug compliance**

The investigator should instruct the patient to take the study drug exactly as prescribed (promote compliance).

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

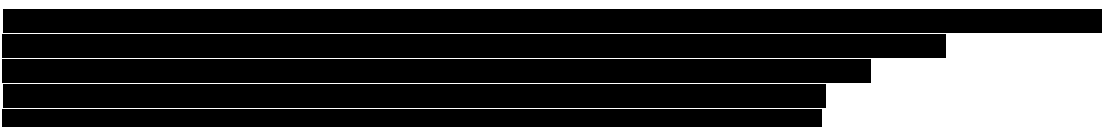
#### **6.5.4.2 Study drug accountability**

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability ledger. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability ledger to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

### **6.5.5 Disposal and destruction**

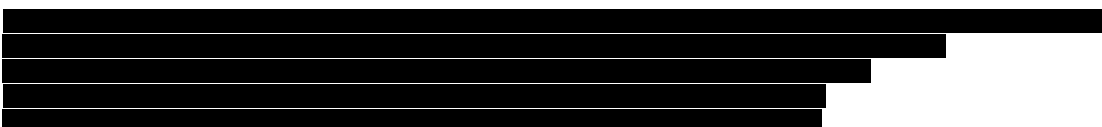
The drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate.



## **7 Visit schedule and assessments**

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

Table 7-1 lists all of the assessments and indicates with an “X”, the visits when they are performed. All data obtained from these assessments must be supported in the patient’s source documentation. The table indicates which assessments produce data to be entered into the database (D) or remain in source documents only (S) (“Category” column).



**Table 7-1 Visit evaluation schedule**

	Category	Reference to Section	Screening	Baseline	Study period											Study Phase Completion	Study Completion
					1	2	3	4	5	6	7	8	9	10	11		
<b>Visit Number</b>			<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>	<b>8</b>	<b>9</b>	<b>10</b>	<b>11</b>	<b>12</b>	<b>13, 14,...<sup>a</sup></b>	<b>776</b>	<b>777</b>
<b>Study Week</b>		<b>7.1.2.</b>	<b>-3 to 0</b>	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>8</b>	<b>12</b>	<b>16</b>	<b>20</b>	<b>24</b>	<b>36</b>	<b>48, 60,...<sup>a</sup></b>	<b>Last dose</b>	<b>Last dose + 4</b>
<b>Study days</b>		<b>7.1.2.</b>	<b>-21 to -1</b>	<b>0</b>	<b>7</b>	<b>14</b>	<b>21</b>	<b>28</b>	<b>56</b>	<b>84</b>	<b>112</b>	<b>140</b>	<b>168</b>	<b>252</b>	<b>336, 420, ....<sup>a</sup></b>	<b>Last dose</b>	<b>Last dose + 28</b>
Obtain Informed Consent	D		X														
Demography	D	7.1.1.2.	X														
Inclusion/exclusion criteria	D		X														
Complete Inclusion / Exclusion Criteria Checklist			X														
Relevant medical history/current medical conditions	D		X														
Physical examination	S	7.2.2.1.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Karnofsky performance status	D	7.2.2.3.	X						X			X	X	X	X	X	
Height	D	7.2.2.1.	X														
Vital signs	D	7.2.2.2.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Gallbladder Ultrasound	D	7.2.2.6.	X						X			X	X	X <sup>b</sup>	X	X	
Hematology, GH, IGF-1	D	7.2.2.4.1, 7.2.2.4.3.	X					X	X	X	X	X	X	X	X <sup>b</sup>	X	
Free T4, TSH	D	7.2.2.4.3.	X						X			X		X <sup>b</sup>	X		
Blood Chemistry (including Total proteins, amylase, lipase, total cholesterol (TC), LDL-cholesterol, triglycerides, sodium, potassium, magnesium, urea, serum creatinine, creatinine clearance)	D	7.2.2.4.3.	X					X	X	X	X	X	X	X	X	X	
LFT (ALT, AST, total bilirubin, Albumin, ALP, and GGT)	D	7.2.2.4.3.	X	X	X	X		X	X	X	X	X	X	X	X	X	



Visit Number	Category	Reference to Section	Screening	Baseline	Study period											Study Phase Completion	Study Completion
					1	2	3	4	5	6	7	8	9	10	11		
<b>Study Week</b>		<b>7.1.2.</b>	<b>-3 to 0</b>	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>8</b>	<b>12</b>	<b>16</b>	<b>20</b>	<b>24</b>	<b>36</b>	<b>48, 60,...<sup>a</sup></b>	<b>Last dose</b>	<b>Last dose + 4</b>
<b>Study days</b>		<b>7.1.2.</b>	<b>-21 to -1</b>	<b>0</b>	<b>7</b>	<b>14</b>	<b>21</b>	<b>28</b>	<b>56</b>	<b>84</b>	<b>112</b>	<b>140</b>	<b>168</b>	<b>252</b>	<b>336, 420, ....<sup>a</sup></b>	<b>Last dose</b>	<b>Last dose + 28</b>
Coagulation (PT, INR)	D	<a href="#">7.2.2.4.2.</a>	X	X	X	X		X	X	X			X	X	X	X	
Fasting Blood Glucose	D	<a href="#">7.2.2.4.3.</a>	X		X	X	X	X	X	X	X	X	X	X	X	X	
Fasting Insulin	D	<a href="#">7.2.2.4.3.</a>	X			X		X	X	X	X	X	X	X	X	X	
HbA <sub>1c</sub>	D	<a href="#">7.2.2.4.3.</a>	X					X		X			X	X	X	X	
Vitamin B12	D	<a href="#">7.2.2.4.3.</a>	X							X			X			X	
Urinary free cortisol and urine creatinine	D	<a href="#">7.2.1.1.1.</a>	X					X	X	X	X	X	X	X	X	X	
Serum cortisol	D	<a href="#">7.2.1.1.2.</a>	X			X		X	X	X	X	X	X	X	X	X	
Plasma ACTH	D	<a href="#">7.2.1.1.2.</a>	X			X		X	X	X	X	X	X	X	X	X	
HbsAg and anti-HCV	D	<a href="#">7.2.2.4.6.</a>	X														
Signs and symptoms of Cushing's disease	D	<a href="#">7.2.1.1.3.</a>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Cushing's syndrome HRQoL and WPAI-GH questionnaire	D	<a href="#">7.2.1.1.4</a> <a href="#">7.2.1.1.5.</a>		X				X		X			X	X	X	X	
Urinalysis	D	<a href="#">7.2.2.4.4.</a>	X							X			X	X	X <sup>b</sup>	X	
Serum Pregnancy test	D	<a href="#">7.2.2.4.5.</a>	X							X					X	X	
ECG	D	<a href="#">7.2.2.5.1.</a>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events	D	<a href="#">8.1.</a>	Continuously														
Prior/Concomitant medications	D	<a href="#">6.3.</a>	X	Continuously													
Drug administration	D	<a href="#">6.1.</a>	Continuously														
Study phase completion record	D	<a href="#">7.1.3.</a>														X	
Study completion record	D	<a href="#">7.1.4.</a>															X

[Redacted text block]



	Category	Reference to Section	Screening	Baseline	Study period											Study Phase Completion	Study Completion
<b>Visit Number</b>			1	2	3	4	5	6	7	8	9	10	11	12	13, 14,... <sup>a</sup>	776	777
<b>Study Week</b>		7.1.2.	-3 to 0	0	1	2	3	4	8	12	16	20	24	36	48, 60,... <sup>a</sup>	Last dose	Last dose + 4
<b>Study days</b>		7.1.2.	-21 to -1	0	7	14	21	28	56	84	112	140	168	252	336, 420, .... <sup>a</sup>	Last dose	Last dose + 28

<sup>a</sup> One visit every 12 weeks/84 days until patients are transitioned to commercial pasireotide or until 31 December 2015 (until 31 December 2016 for sites in South Korea and Brazil), whichever comes first

<sup>b</sup> To be done every 24 weeks after visit 13

D Data/assessments to be entered in the database

S Data/assessments that remain in source documents only, not to be recorded on CRF



### **7.1.1 Screening**

After the informed consent is obtained, screening evaluations will be performed to assess eligibility for study entry prior to administration of any study drug (Week -3 to 0).

Informed consent must be obtained before starting the washout periods for the drugs indicated in the protocol. The washout period for the drugs indicated in the inclusion criteria need to be completed before urine, blood and saliva collections at screening are started.

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

In order to determine and confirm the eligibility of the patient, when all screening procedures are complete, a key eligibility checklist must be completed manually 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 into the trial. This checklist must be submitted to the sponsor for approval prior to study enrollment.

#### **7.1.1.1 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 not being started on treatment will be entered on the Screening Log Page. The demographic information, must also be completed for Screen Failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a Serious Adverse Event during the Screening Phase (see [Section 8](#) for SAE reporting details).

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

Standard demographic information and medical history will be collected at visit 1. Cushing's disease history and DM history together with the medication/treatment used will be collected.

### **7.1.2 Treatment period**

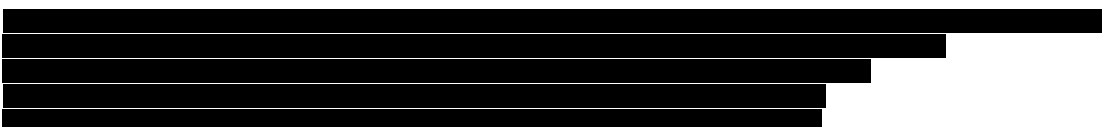
Patients will be treated until the drug is approved for commercial use and reimbursed in each respective country or until 31 December 2015 (until 31 December 2016 for sites in South Korea and Brazil), whichever occurs first.

Patients who are transitioned to commercial pasireotide s.c. will be considered as completed as per protocol requirements (refer to [Section 6.1.2](#)).

All visits should be performed on the indicated days. Should this not be possible, the following visit windows apply: +/- 2 days from visit 3 to 11 and +/- 5 days from visit 12 onwards. The Study Phase Completion visit has to be performed on the day of the last study drug administration (+ 5 days). The Study Completion visit has to be performed 28 days (+/- 5 days) after the patient received the last pasireotide s.c. dose.

#### **7.1.3 Study phase completion visit, including premature withdrawal and study discontinuation visit**

Patients who permanently discontinue the study drug should be considered prematurely discontinued from the study Patients will have to perform a study phase completion



evaluation on the day of the last study drug administration (refer to Study Phase Completion evaluation in [Table 7-1](#)).

If a 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 Phase Completion CRF page. If patients refuse to return for these visits or are unable to do so, every effort should be made to contact them.

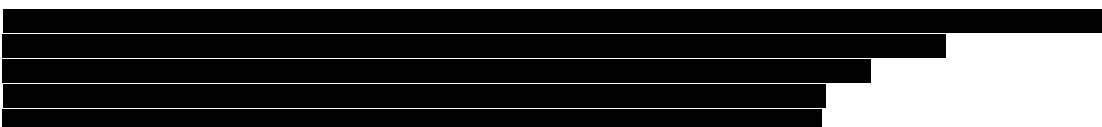
Patients who complete the study because they are transitioned to commercial pasireotide or patients who are treated until 31 December 2015 (until 31 December 2016 for sites in South Korea and Brazil) will have to perform a study phase completion evaluation on the day of the last study drug administration (refer to Study Phase Completion evaluation in [Table 7-1](#)). A Study Phase Completion CRF page has to be completed.

### 7.1.3.1 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:

- Patients experiencing unacceptable drug-related toxicity (as described in [Table 6-1](#))
- 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 HbA<sub>1c</sub> value  $\geq$  10 % despite prior appropriate management and prior dose adjustment of the study drug,
- Patients experiencing adverse events in QTc:
  - a confirmed QTcF > 480msec and discontinuation recommended by a cardiologist, or
  - Mean QTcF > 500msec measured by triplicate ECGs and confirmed by a cardiologist
  - Significant arrhythmia findings from Holter monitoring such as:
    1. Any ventricular or supra-ventricular tachyarrhythmia associated with symptoms of hemodynamic compromise
    2. Sustained ventricular tachycardia (>30 sec) irrespective of symptoms
    3. Recurrent non-sustained VT ( $\geq$  3 beats) during any 24-hour monitoring period
    4. Torsades de Pointes (TdP)
    5. Cardiac arrest
    6. Pause >5 seconds
    7. Second or third degree AV block
  - New occurrence of clinically significant/symptomatic bradycardia, or
  - Increased risk of QT prolongation by use of medications with known risk of TdP, or
  - Hypokalemia (<3.5 mmol/L) or hypomagnesaemia (<0.5 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 hypoadrenalism: defined as an early morning (between 8 and 10 am) serum cortisol < 3  $\mu$ g/dL and a mean 24h-UFC measurement < LLN or symptoms suggestive of



- hypoadrenalism (e.g. postural hypotension, nausea, and abdominal pain) in association with a mean 24h-UFC measurement < LLN, which persist after drug dose adjustment
- Lack of efficacy: consistently elevated mean 24h-UFC level and lack of clinical benefit after  $\geq 3$  months treatment
  - Pregnancy
  - Patient experiencing
    - ALT or AST > 3 x ULN and Total Bilirubin  $\geq 2$  x ULN and ALP < 2 x ULN
    - ALT or AST > 5 x ULN and  $\leq 8$  x ULN persistent for more than 2 weeks
    - ALT or AST > 8 x 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 outlined in [Section 6.2.1.1](#). 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:

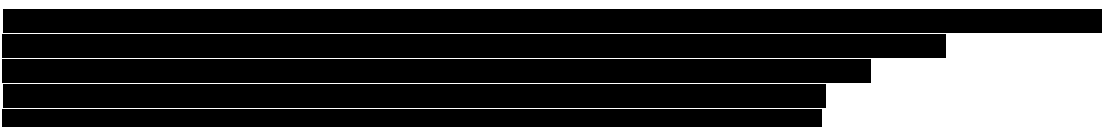
- Adverse event(s)
- Abnormal laboratory value(s)
- Abnormal test procedure result(s)
- Protocol violation
- Subject withdrew consent
- Lost to follow-up
- Administrative problems
- Death

#### **7.1.4 Follow up period**

All patients must have a safety evaluation during the Study Completion visit, 28 days after the last dose of study treatment.

A Study Completion CRF page should be completed giving the date and reason for stopping the study treatment.

Patients lost to follow up should be recorded as such on the CRF. For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.



## 7.2 Assessment types

### 7.2.1 Efficacy assessments

#### 7.2.1.1 Secondary parameters

##### 7.2.1.1.1 Mean 24-hour urinary free cortisol (UFC)

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). 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 intervals until week 24. At week 4, 8, 16 and 20, mean 24h-UFC will be determined from two 24-hour urine collections collected on two consecutive days occurring before the visit. At week 12, 24 and 48, the mean 24h-UFC from three 24-hour urine collections, collected over the week before the visit, will be determined. After week 24, the mean 24h-UFC will be determined at 12-week intervals until end of study visit, from two 24-hour collections during two consecutive days prior to each respective visit (except at Week 48). For each sample, the first urine of the day will be discarded, all subsequent urine has to be collected in the specimen container, including the last urine of the 24-hr period. The urine sample will be checked for volume and creatinine will be measured from the urine sample by the central laboratory.

UFC will be determined by LC/MS/MS. The normal ranges will be determined by the central laboratory's own reference range. All samples, including screening samples, will be analyzed by a central laboratory. Procedures for sample collection, handling, storage and transportation will be provided in detail to the sites by the central laboratory.

##### 7.2.1.1.2 Serum cortisol and plasma ACTH

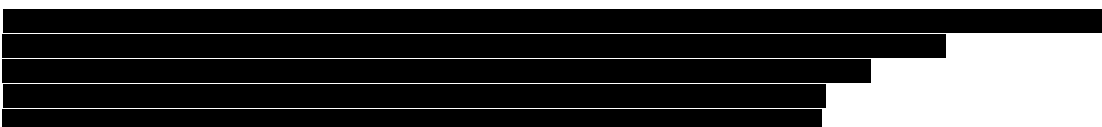
A predose blood draw for plasma ACTH and serum cortisol assessment will be taken. Blood samplings will be done as indicated in [Table 7-1](#). Procedures for sample drawing, handling, storage and transportation will be provided by the central laboratory.

##### 7.2.1.1.3 Clinical signs and symptoms

The following clinical signs and 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:  $\text{mean BP} = \text{DBP} + [(\text{SBP} - \text{DBP})/3]$ . 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 repeat measurements are to be made at one- to two-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 all indicated visits. 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.

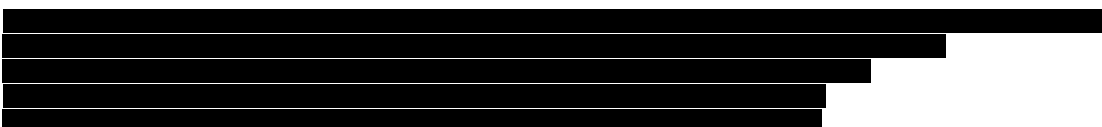
### **Facial rubor, hirsutism, striae, bruising and supraclavicular and dorsal fat pad**

These signs and symptoms will be evaluated by the investigator as per visit evaluation schedule (refer to [Table 7-1](#)). For assessment of hirsutism, the Ferriman-Gallway score, a method of evaluating and quantifying hirsutism in women, will be used. Female patients will be asked not to shave during 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

#### 7.2.1.1.4 Quality of Life

A Cushing's syndrome HRQoL questionnaire (CushingQOL, [Webb et al 2008](#)) will be used in this study to monitor patients' HRQoL. This questionnaire will be completed by the patient as per visit evaluation schedule (refer to [Table 7-1](#)).

#### 7.2.1.1.5 Work Productivity and Activity Impairment – General Health Questionnaire

The Work Productivity and Activity Impairment – General Health (WPAI-GH) questionnaire will be used in this study to assess patient-reported quantitative assessment of the amount of absenteeism, presenteeism, and daily activity impairment attributable to their disease. This questionnaire will be completed by the patient as per visit evaluation schedule (refer to [Table 7-1](#)).



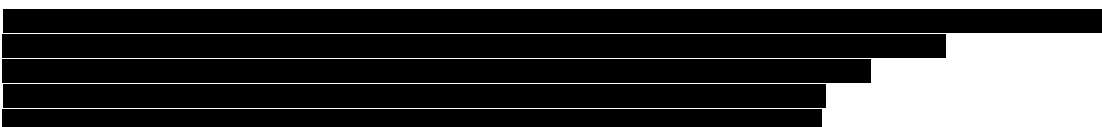
## 7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing the evaluations described below and the collection of adverse events at every visit. For details on AE collection and reporting, refer to [Section 8](#).

### 7.2.2.1 Physical examination, height

A complete physical examination will be performed by the investigator at every visit. Height will be recorded at visit 1 only.

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.

If, at visit 2, the complete physical examination occurred within the last 4 days of the baseline visit, it does not have to be repeated at baseline.

#### **7.2.2.2 Vital signs**

Blood pressure, body temperature and heart rate will be measured at every visit and recorded in the CRF.

#### **7.2.2.3 Performance status**

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

#### **7.2.2.4 Laboratory evaluations**

The following laboratory evaluations will be performed during the study:

##### **7.2.2.4.1 Hematology**

Hematology assessment will include: hemoglobin, hematocrit, red blood cell count, platelets, total white blood cell count (WBC) absolute & differential including neutrophils, lymphocytes, monocytes, eosinophils, basophils.

##### **7.2.2.4.2 Coagulation**

The prothrombin time (PT) will be reported in seconds and as international normalized ratio (INR).

##### **7.2.2.4.3 Clinical chemistry**

The following tests will be performed at each scheduled visit as indicated in [Table 7-1](#): total proteins, amylase, lipase, total cholesterol (TC), LDL-cholesterol, triglycerides, sodium, potassium, magnesium, urea, serum creatinine, creatinine clearance, thyroid function test (free T4 and TSH), fasting blood glucose, fasting insulin, glycosylated hemoglobin (HbA<sub>1c</sub>), and assessment of Vitamin B12, GH and IGF-1.

#### **Liver function tests (LFT)**

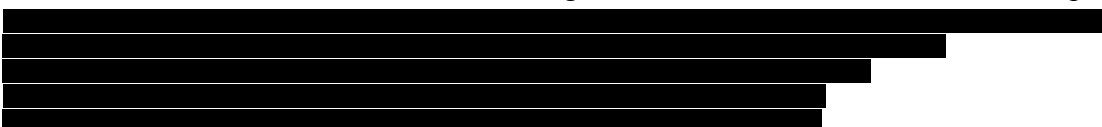
LFT will be performed at each scheduled visit as indicated in [Table 7-1](#) and will include ALT, AST, total bilirubin, albumin, ALP, and GGT.

##### **7.2.2.4.4 Urinalysis**

A urinalysis test (specific gravity, pH, glucose, proteins, bilirubin, ketones, leucocytes, and blood) is required as per [Table 7-1](#).

##### **7.2.2.4.5 Pregnancy test**

For women of childbearing potential, a serum pregnancy test ( $\beta$ -HCG) will be performed as indicated in [Table 7-1](#). During treatment, an additional test will be performed if menses are





delayed for more than 7 days. In case of pregnancy, patients must be withdrawn from the study.

#### 7.2.2.4.6 Serology

Hepatitis B surface antigen (HbsAg) as well as Hepatitis C antibody (anti-HCV) test will be performed at screening.

### 7.2.2.5 Cardiac assessments

#### 7.2.2.5.1 Electrocardiogram (ECG)

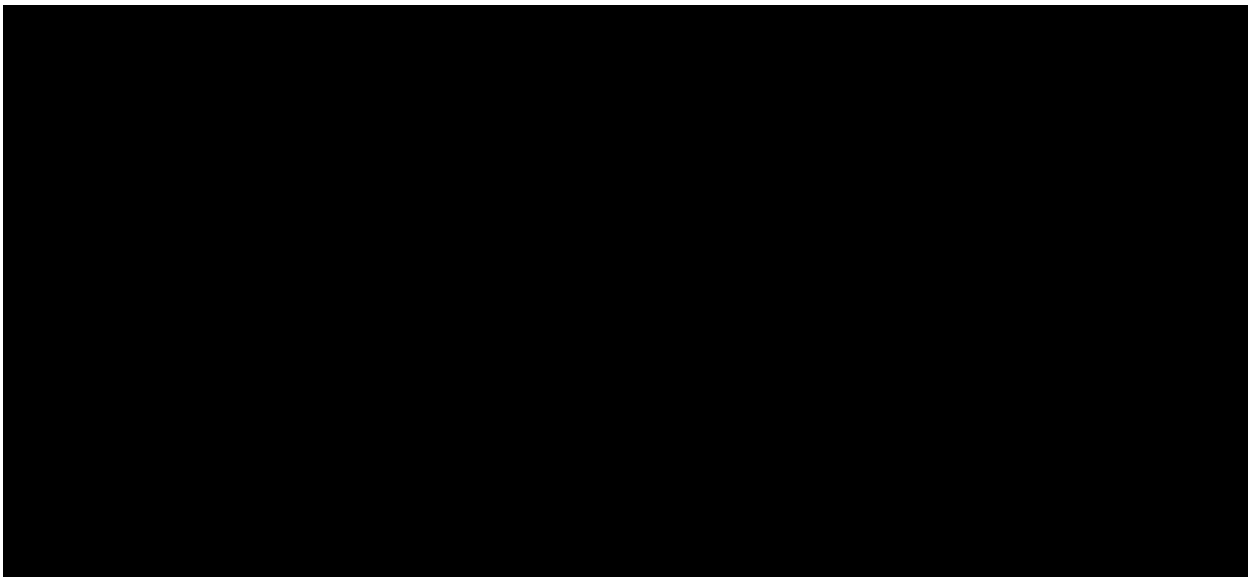
A 12-lead ECG will be performed at the sites, in lying position, at all indicated visits as per [Table 7-1](#).

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 evaluated locally.

Interpretation of the tracing must be made by a qualified physician and documented on the ECG CRF page. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities present when the patient signed informed consent should be reported on the Medical History CRF page. Clinically significant findings must be discussed with the Medical Monitor prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events CRF page. In case of confirmed QTcF > 480msec, a Holter ECG will be required for patients continuing in the study (described in [Section 6.2.1.1](#)).

#### 7.2.2.6 Gallbladder ultrasound

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



## **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 under the signs, symptoms or diagnosis associated with them. Conditions that were already present at the time of informed consent should be recorded in the Medical History CRF.

Adverse event monitoring and reporting will be continued for at least 28 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 3.0. 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

[REDACTED]

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 relationship to the study drug (suspected/not suspected)
3. Its duration (start and end dates or if continuing at final exam)
4. Action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. Whether it is serious, where a serious adverse event (SAE) is defined as per [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.

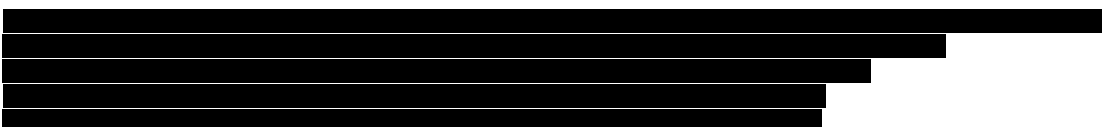
Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

## **8.1.2 Laboratory test abnormalities**

### **8.1.2.1 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 and is still, by definition, an adverse event.



## 8.2 Serious adverse events

### 8.2.1 Definitions

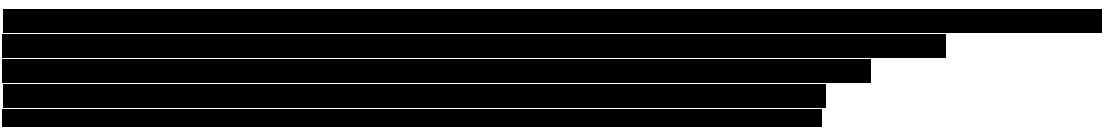
Serious adverse event (SAE) is defined as one of the following:

- 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, unless hospitalization is for:
  - 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
  - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Protocol exempt SAEs: SAEs specifically defined in the protocol and where there has been a clear agreement with regulators not to collect these SAEs in the safety database, provided the information is collected elsewhere. For example, this may include serious adverse events that are also a primary outcome measure, such as mortality, survival rate or number of flares of the condition being studied.

### 8.2.2 Reporting

To ensure patient safety, every SAE, **regardless of suspected causality**, occurring after the patient has provided informed consent and until 28 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 28 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 oncology Novartis Drug Safety and Epidemiology (DS&E) department.



The telephone and telefax number of the contact persons in the local department of Drug Safety and Epidemiology (DS&E), specific to the site, are listed 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.

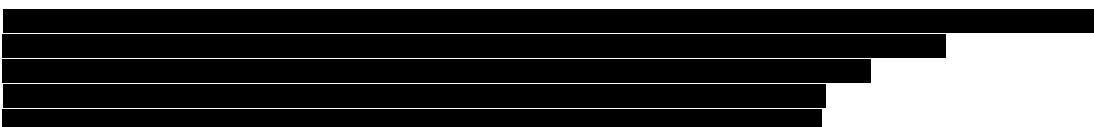
Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original 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.

In addition, for Pasireotide s.c the following events are of special interest for targeted follow-up and should be notified to Novartis DS&E in the same manner as a SAE.

- Arrhythmogenic
- Bradycardia
- Coagulation
- Constipation
- Convulsions
- Diabetes insipidus
- Diarrhoea
- Gallbladder and biliary related AEs
- GI bleeding
- Growth hormone deficiency
- Hyperglycemia
- Hypocalcemia
- Hypocortisolism
- Hypotension
- Hypothyroidism
- Injection site reaction
- Liver safety
- Low blood cell
- Nausea
- Pancreatitis
- QT-prolongation
- Rhabdomyolysis

### **8.3 Emergency unblinding of treatment assignment**

Not applicable.



## **8.4 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 Drug Safety and Epidemiology (DS&E) 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.

## **8.5 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 IB 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.

## **8.6 Data Monitoring Committee**

No Data monitoring Committee will be established in this study.

## **8.7 Steering Committee**

No Steering Committee will be established in this study.

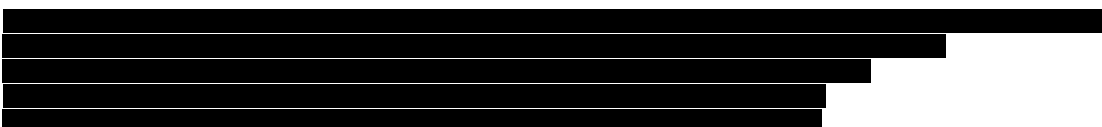
# **9 Data collection and management**

## **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 at least vital status (i.e. that the subject is alive) 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 in CRFs 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 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.

The results of laboratory/Biomarker samples processed centrally will be sent electronically to Novartis (or a designated CRO) for inclusion in the clinical database.

At the conclusion of the study, the occurrence of any protocol violations will be determined. After this action has 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.

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

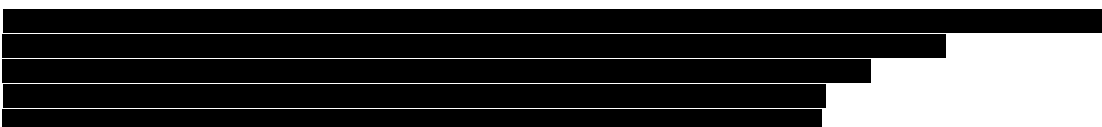
Data will be analyzed by Novartis and/or a designated CRO. It is planned that the data from all centers that participate in this protocol will be used. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

Final analyses will be performed when all patients have been followed for 28 days after they have either prematurely discontinued pasireotide s.c. or after completing treatment as per protocol (i.e. when the study drug is approved for commercial use and reimbursed in each respective country or until 31 December 2015 (until 31 December 2016 for sites in South Korea and Brazil), whichever occurs first).

### 10.1 Analysis sets

#### 10.1.1 Full Analysis Set

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





### **10.1.2 Safety Set**

The safety set includes all patients who received at least one dose of pasireotide s.c. and had at least one post-baseline safety assessment.

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

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

Demographic and other baseline data (including disease characteristics) will be summarized descriptively for the FAS. Categorical data will be presented as frequencies and percentages. For continuous data, the mean, standard deviation, median, minimum, and maximum will be presented.

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

Descriptive statistics will be used to summarize the mean daily dose and duration of pasireotide s.c. 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.

### **10.4 Primary objective**

Refer to [Section 3](#).

#### **10.4.1 Variable**

The primary variable is the proportion of patients having a drug-related adverse event that was recorded as grade 3 or 4, or as a serious adverse event.

The analysis of the primary variable is described in [Section 10.5.2.2](#).

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

No statistical hypotheses are being tested in this study.

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

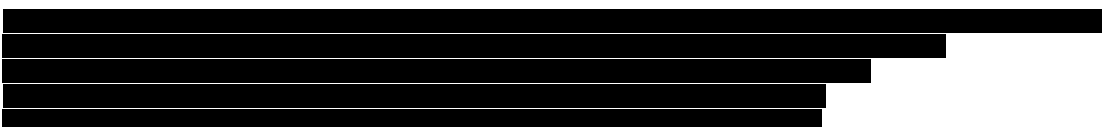
Not applicable. All attempts will be made to ensure that the database contains full information for all safety data.

#### **10.4.4 Supportive analyses**

Not applicable.

### **10.5 Secondary objectives**

Refer to [Section 3](#).



### **10.5.1 Secondary efficacy variables**

The secondary efficacy analysis will be performed on the FAS. Unless noted otherwise, missing values will not be imputed in these analyses. The parameters assessed at screening and not at baseline are to be considered as baseline.

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

The number and percentage with corresponding exact two-sided 95% CI of patients achieving normalization of mean 24h-UFC (i.e. mean 24h-UFC  $\leq$  1.0xULN) at Week 12, 24 and 48 (separately) will be presented.

If Week 24 mean 24h-UFC is missing then it will be imputed by the last available mean 24h-UFC of at least two samples between and including Week 12 and Week 24, and if Week 48 mean 24h-UFC is missing then it will be imputed by the last available mean 24h-UFC of at least two samples between and including Week 12 and Week 48. Summaries with and without imputing missing Week 24 and Week 48 mean 24h-UFC will be presented.

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

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

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

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

#### **10.5.1.3 Change from baseline in mean 24h-UFC to Week 12, 24 and 48**

Descriptive summaries of actual and percentage change with corresponding two-sided 95% CIs in mean 24h-UFC from baseline to Week 12, 24 and 48 will be provided.

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

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

Descriptive summaries of actual and percentage change in mean GH and IGF-1 values from baseline to Week 12, 24 and 48 will be provided.

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

#### **10.5.1.5 Clinical signs and symptoms**

The following clinical signs of Cushing's disease will be assessed by descriptive summaries of the change in systolic BP (standing and sitting), diastolic BP (standing and sitting), BMI, waist circumference and weight from baseline to each post-baseline visit. In addition, the proportion of patients satisfying the clinically relevant thresholds specified in the following

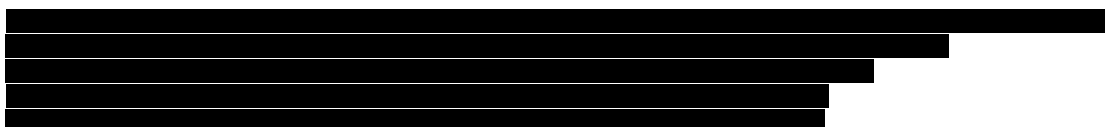
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table will be calculated along with the exact two-sided 95% CIs at each scheduled post-baseline assessment.

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

The following clinical signs and symptoms of Cushing’s disease will be assessed by descriptive summaries of changes and shifts from baseline to each scheduled post-baseline assessment. The clinical signs and symptoms that will be analyzed and the corresponding methods of analyses are provided in the following table.

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



## 10.5.2 Safety objectives

### 10.5.2.1 Analysis set and grouping for the analyses

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

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

1. Pre-treatment period: from day of patient's informed consent to the day before first dose of study medication,
2. On-treatment period: from day of first dose of study medication to 28 days after last dose of study medication
3. Post-treatment period: starting at 29 days after last dose of study medication

### 10.5.2.2 Adverse events (AEs)

The definition of an adverse event for this study can be found in [Section 8.1](#).

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

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

In addition, the incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and/or preferred term, severity (based on CTCAE grades), type of adverse event and relation to study treatment. Deaths will be listed and summarized by cause of death.

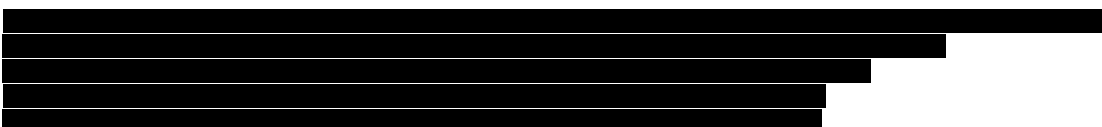
### 10.5.2.3 Laboratory abnormalities

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

For laboratory tests covered by the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, the study's biostatistics and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used. In the unlikely case when a laboratory normal range overlaps into the higher (i.e. non-zero) CTC grade, the laboratory value will still be taken as within normal limits and assigned a CTC grade of zero.

For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges. The following summaries will be produced for the laboratory data (by laboratory parameter):

- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value,



- For laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high classification to compare baseline to the worst on-treatment value,
- Shift tables of fasting glucose and related biochemical parameters using the ADA (2010) or similar low/normal/high classifications to compare baseline to the worst and last on-treatment value.

The following listings will be produced for the laboratory data:

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

#### **10.5.2.4 Other safety data**

##### **Vital signs**

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

The criteria for clinically notable abnormalities are defined as follows:

##### **Clinically notable elevated values**

- Systolic BP:  $\geq 180$  mmHg and an increase  $\geq 20$  mmHg from baseline
- Diastolic BP:  $\geq 105$  mmHg and an increase  $\geq 15$  mmHg from baseline.
- Body temperature:  $\geq 39.1^\circ\text{C}$
- Weight: Increase from baseline of  $\geq 10\%$
- Heart rate:  $\geq 120$  bpm with increase from baseline of  $\geq 15$  bpm

##### **Clinically notable below normal values**

- Systolic BP:  $\leq 90$  mmHg and a decrease  $\geq 20$  mmHg from baseline
- Diastolic BP:  $\leq 50$  mmHg and a decrease  $\geq 15$  mmHg from baseline
- Body temperature:  $\leq 35^\circ\text{C}$
- Weight: decrease from baseline of  $\geq 10\%$
- Heart rate:  $\leq 50$  bpm with decrease from baseline of  $\geq 15$  bpm

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

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



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

### **10.5.3 Resource utilization**

Not applicable

### **10.5.4 Patient-reported outcomes**

#### **Cushing's syndrome HRQoL questionnaire**

A 12-item Cushing's syndrome HRQoL questionnaire (CushingQoL) is implemented in this trial. Raw summative scores are calculated and standardized on a by-patient and visit basis.

Patients who completed 9 or more items at an assessment are considered evaluable for that visit. Standardized scores and their changes from baseline to each scheduled post-baseline assessment will be descriptively summarized.

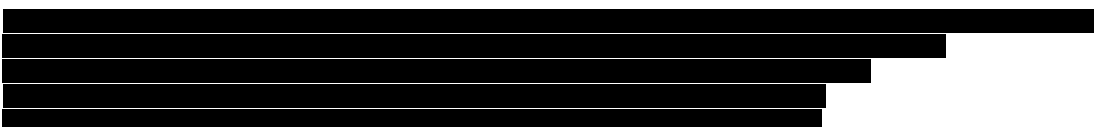
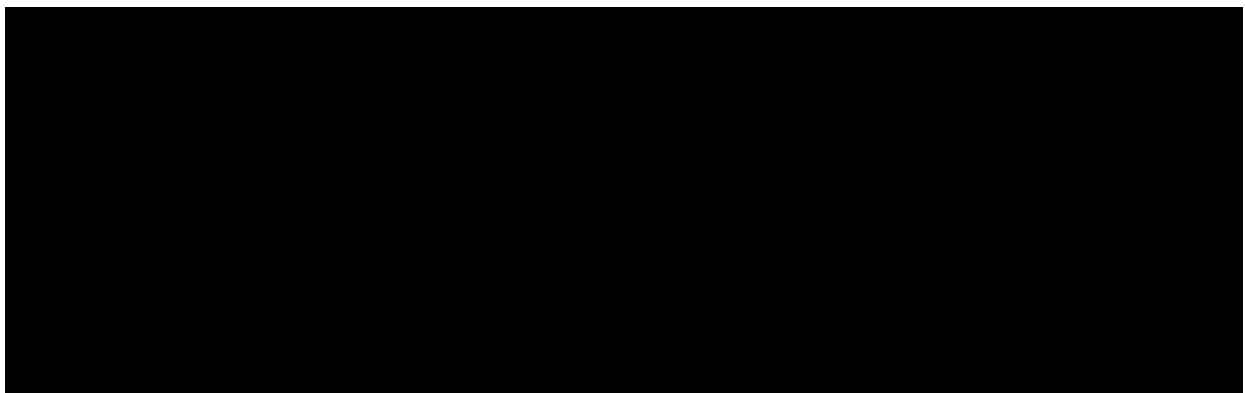
#### **Work Productivity and Activity Impairment-General Health (WPAI-GH) questionnaire**

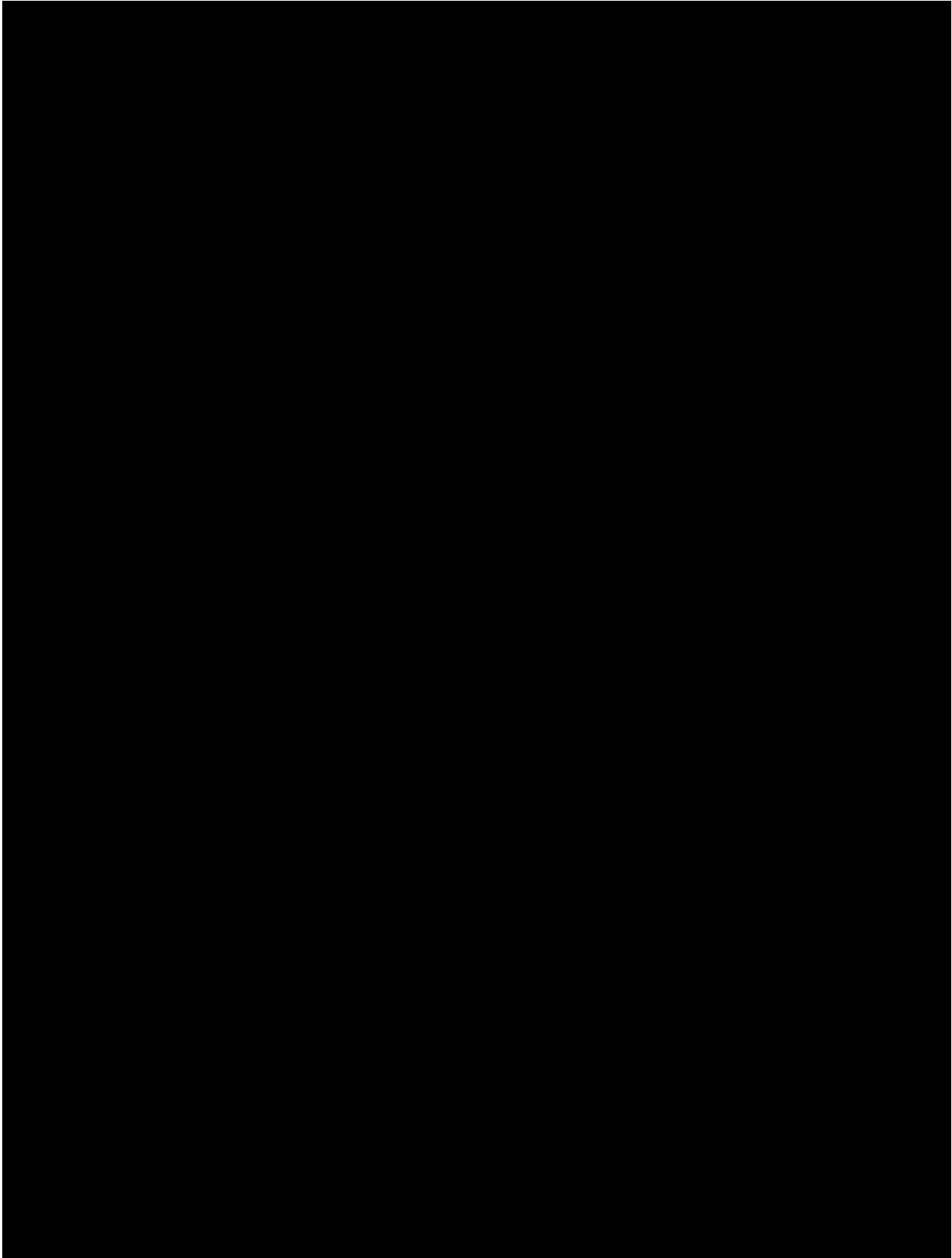
The WPAI-GH yields four types of scores:

1. Absenteeism (work time missed)
2. Presenteeism (impairment at work / reduced on-the-job effectiveness)
3. Work productivity loss (overall work impairment / absenteeism plus presenteeism)
4. Activity Impairment

WPAI-GH scores are based on 1-item (presenteeism, activity impairment), 2-items (absenteeism) and multiple items (overall work productivity); a score will not be calculated if there is a missing response to the corresponding item. For example, an analysis of absenteeism would include only those subjects with responses to hours missed and to hours worked.

WPAI-GH scores and their changes from baseline to each scheduled post-baseline assessment will be descriptively summarized.





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## 10.7 Interim analysis

No formal interim analysis is planned. However, since the timing of drug approval may differ between regions, data from a specific region may be reported when all patients from that region have been followed for 28 days after they have either prematurely discontinued pasireotide s.c. or after completing treatment as per protocol (i.e. when the study drug is approved for commercial use and reimbursed in each respective country or until 31 December 2015 (until 31 December 2016 for sites in South Korea and Brazil), whichever occurs first). For regulatory purposes, at time of a regional interim analysis, data from countries where the trial is still ongoing maybe included. Furthermore, independent of a regional interim analysis additional interim analysis may be performed for regulatory purpose or publication purpose and details will be specified in the study's analysis plan.

## 10.8 Sample size calculation

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

## 10.9 Power for analysis of key secondary variables

Not applicable.

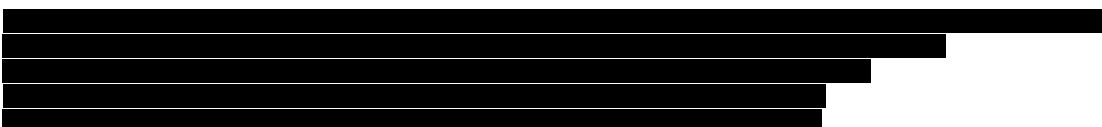
## 11 Ethical considerations and administrative procedures

### 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. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before study initiation. 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 or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. 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 investigators in a separate document with 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 was 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**

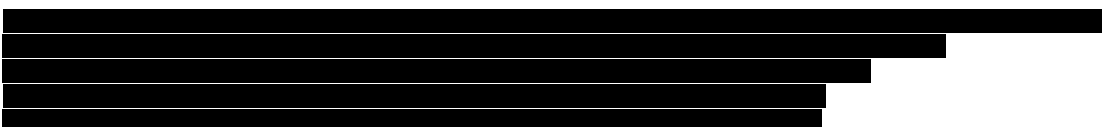
Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in [Section 4.4](#).

### **11.5 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](http://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. Different publications of the data are planned. Regional and/or country population analysis and publication will be allowed after the analysis and presentation of the multinational (or global) population is performed.

### **11.6 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 study 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. For electronic CRFs an audit trail will be maintained by the system. 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.

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

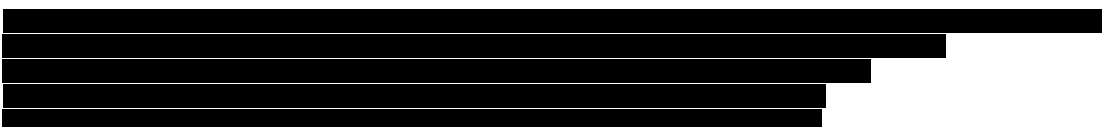
The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

### **11.8 Audits and inspections**

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

### **11.9 Financial disclosures**

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

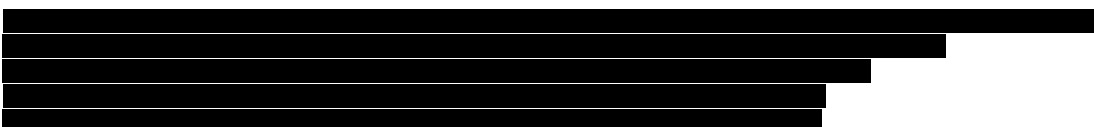


## **12 Protocol adherence**

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/REB at the study site should be informed within 10 working days.



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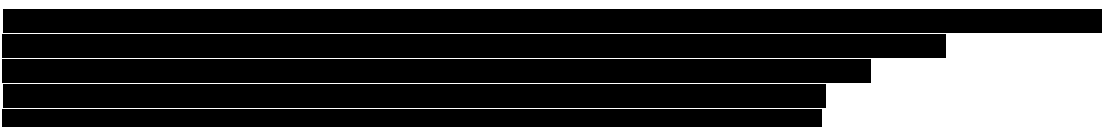
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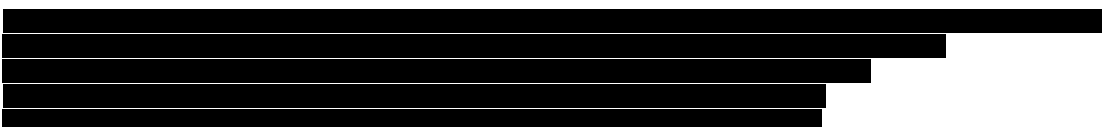
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