Recordati Research and Development

SOM230 (pasireotide)

Clinical Trial Protocol CSOM230B2412

An open label, multi-center pasireotide roll-over protocol for patients who have completed a previous Novartis-sponsored pasireotide study and are judged by the investigator to benefit from continued pasireotide treatment

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List of abbreviations

AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
b.i.d.	twice a day
bpm	Beats per minute
CD	Cushing's disease
CMO&PS	Chief Medical Office & Patient Safety
CRO	Contract Research Organization
CSR	Clinical study report
ECG	Electrocardiogram
eCRF	Electronic Case Report/Record Form
EDC	Electronic Data Capture
FPFV	First Patient First Visit
FPG	Fasting plasma glucose
GDD	Global Drug Development
GH	Growth Hormone
GIP	Glucose-dependent insulinotropic peptide
GLP-1	Glucagon-like peptide-1
HBsAG	Hepatitis B surface antigen
HCV	Hepatitis C virus
IB	Investigators Brochure
ICH	International Conference on Harmonization
IGF-1	Insulin-like growth factor 1
i.m.	Intramuscular
IRB	Institutional Review Board
IEC	Independent Ethics Committee
i.v.	Intravenous(ly)
LAR	Long Acting Release
MCC	Merkel cell carcinoma
MTD	Maximum tolerated dose
mUFC	Mean urinary free cortisol
NETs	Neuroendocrine tumors
OGTT	Oral Glucose Tolerance Test
PK	Pharmacokinetic
pNET	Pancreatic neuroendocrine tumors
q.d.	Once per day
QTcB	QT corrected (Bazett)
QTcF	QT corrected (Fridericia)
QTcI	QT corrected (individualized)
REB	Research Ethics Board
SAE	Serious adverse event
s.c.	Subcutaneous
SSA	Somatostatin analog
sst123	Somatostatin receptor subtypes
sst5	Somatostatin receptor subtypes

TdP	Torsades de pointes
ULN	Upper limit of normal

Glossary of terms

Assessment	A procedure used to generate data required by the study
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Patient Number	A unique identifying number assigned to each patient who enrolls in the study
Parent study	The original Novartis-sponsored study where the patient was first enrolled and received pasireotide treatment.
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
Roll-over study	A roll-over study allows patients from multiple parent studies spanning multiple indications to continue to be treated within one study after the completion of the parent study/ies
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

Amendment 5 (02-Nov-2021)

Amendment rationale

It is anticipated that pasireotide will not be commercially available and reimbursed in all participating countries at study end. In order to ensure that patients deriving clinical benefit from pasireotide will continue receiving treatment with this drug outside the frame of the clinical trial, they will be allowed to obtain pasireotide through country-specific programmes as soon as they become available – even prior to the end of the study. This will ensure treatment continuity.

The following protocol amendment is applicable to Brazil, France, Germany, India, Italy, Malaysia, Mexico, Peru and Thailand.

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 underline for insertions.

1. Section 4.3: Definition of end of the study: the language was updated to state that even prior to the end of this study, patients will be allowed to receive pasireotide through country-specific programmes outside the frame of this clinical trial.
2. Section 7.1.3: Treatment period: updated language to clarify that even prior to the end of this study, patients will be allowed to receive pasireotide through country-specific programmes outside the frame of this clinical trial.
3. Section 7.1.5.1: Criteria for premature withdrawal: added language confirming that– even prior to the end of the study- patients will be allowed to receive pasireotide outside the frame of this clinical trial through country-specific programmes.

IRBs/IECs

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

The changes described in this amended protocol are substantial and do require IRB/IEC approval prior to implementation.

Amendment 4 (06 May-2020)

Amendment rationale

Novartis has signed an agreement to transfer the worldwide rights of Signifor® and Signifor® LAR to Recordati. Within the framework of such agreement, the two Companies agreed a sponsorship transfer of this study with pasireotide from Novartis to Recordati.

The purpose of this substantial amendment is to reflect the change in sponsorship, and to add IQVIA as the CRO in charge for performing some trial-related activities on behalf of Recordati.

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 underline for insertions.

- All sections: were updated to substitute the name of the current sponsor Novartis with the name of the new sponsor Recordati or of IQVIA on behalf of Recordati, as applicable.

IRBs/IECs

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

The changes described in this amended protocol are substantial and do require IRB/IEC approval prior to implementation.

Amendment 3 (08-Mar-2019)

Amendment rationale

The main purpose of this amendment is to:

- Update the trial selection criteria to allow patients from Novartis-sponsored trials, being treated with pasireotide alone or in combination with another treatment for Cushing's Disease and Acromegaly, to participate in this study. Several of the participating parent protocols permit for pasireotide to be administered in combination with another medical therapy. Revising the selection criteria would ensure those patients receiving clinical benefit would have continued access to the combination treatment. Combination treatment through this rollover would only be available for patients with Cushing's Disease or Acromegaly.

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 underline for insertions.

1. Protocol summary: Removed the exclusion criteria related to patients participating in combination treatment studies.
2. Protocol summary: In the Investigational and reference therapy section – Combination therapy as per the parent protocol wording added.
3. Section 1.2.1.2.1: Updated wording to include results from SOM230G2304 and SOM230C2402 trials that are now completed.
4. Section 2.3 Rationale for dose and regimen selection: Language added to clarify that any medication given in combination with pasireotide must follow the dose ranges and regimen of the parent protocol.
5. Section 2.4 Rationale for choice of combination drugs: language added to clarify that patients have been receiving combination treatment in the parent studies or an additional medication for acromegaly or Cushing's disease have been added based on the investigator's opinion. Rationale language for cabergoline treatment was also added.
6. Section 4.1: Deleted repetitive language
7. Figure 4-1: Updated to add combination treatment language
8. Section 5.3 Exclusion Criteria: Removed exclusion criteria number 2 related to patients participating in combination treatment.
9. Section 6.1.2: Added section regarding dosing regimen for patients on combination treatment with cabergoline.
10. Section 6.1.3: Added section regarding dosing guidelines for combination treatment.
11. Section 6.1.7: Repetitive language deleted
12. Section 6.2.1: Starting dose rationale: Language added to clarify that the starting dose of any medication given in combination with pasireotide must follow the last dose given in the parent protocol.
13. Section 6.4.2: removed section as not applicable as this trial does not have randomization.
14. Section 6.5.1: Updated to add language for combination treatment

15. Table 6-2: Dose strengths added for both pasireotide LAR and s.c.
16. Table 6-3: Updated to add wording on combination treatment storage
17. Section 7.1.3 Treatment Period: Corrected the timing of the visits to quarterly visits every 12 weeks +/- 2 weeks.
18. Section 8.1.1 Definitions and Reporting: Updated the language to define the safety reporting period as 30 days for s.c. formulation of pasireotide and 84 days for LAR formulation.
19. Appendix 12 Dose modification information for patients with Cushing's receiving pasireotide s.c in combination with cabergoline (SOM230B2411): The appendix added to provide guidance of permitted doses and dose modifications.

IRBs/IECs

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.

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 protocol amendment.

Amendment 2 (29-Sep-2017)

Amendment rationale

The main purpose of this amendment is to:

- Include language on the trial end date to meet the regulatory guidelines of the Medicine and Health Research Authority (MHRA), in the United Kingdom (UK).
- This trial was deemed to be a voluntary PASS (post-authorization safety study) by Novartis Regulatory Affairs in 2016. An interim analysis will be performed in 2017, and every 2 years thereafter, until the final database lock.
- This amendment will also help to clarify the visit schedules for patients taking pasireotide s.c. and those taking pasireotide LAR, and further highlights the required timelines for using highly effective methods of contraception after last dose of study medication.

This roll-over study has been opened since 10-Jun-2013 and has enrolled a total of 301 patients with 259 patients ongoing.

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 underline for insertions.

- Protocol Summary, Study Design Section: A trial end date was added for the UK.
- Section 2.1 Study Rationale: Updated the language to clarify that patients will continue to receive study drug as long as the patient continues to receive clinical benefit as judged by the Investigator or one of the discontinuation criteria is met.
- Section 4.1 Description of study design: Clarified that all patients can begin treatment with study drug as soon as they enter the trial and that all patients are expected to report to the study site for the first visit to begin study participation.
- Section 4.1 Description of study design: Clarified the study visit schedule for patients taking pasireotide LAR versus those taking pasireotide s.c. and the permissible visit windows for those visits.
- Section 4.1 Description of study design: Added language on the trial end date and updated the language that patients will continue to receive pasireotide as long as the patient continues to receive clinical benefit as judged by the Investigator or one of the discontinuation criteria is met.
- Section 4.2 Timing of interim analysis and design adaptations: Added language that an interim analysis will be performed in 2017 and every 2 years thereafter until the final database lock.
- Section 4.3 Definition of end of the study: Updated the language to provide a specific trial end date.
- Section 5.3 Exclusion Criteria: Corrected the timing of the use of highly effective methods of contraception. Contraception must be used for 30 days after the final dose of pasireotide s.c. and 84 days after the final dose of pasireotide LAR.
- Section 6.1.5 Treatment duration: A trial end date was added.

- Section 7.1.3 Treatment period: Clarified the study visit schedule for patients taking pasireotide LAR versus those taking pasireotide s.c. and the permissible visit windows for those visits. The requirement for 5 study visits in the first year was removed as there are no safety concerns with the trial and there was no added value in the patients coming to clinic for an additional visit in the first year.
- Section 7.1.3 Treatment duration: A trial end date was added.
- Section 7.1.4 Pregnancy and assessment of fertility: Corrected the timing of the use of highly effective methods of contraception. Contraception must be used for 30 days after the final dose of pasireotide s.c. and 84 days after the final dose of pasireotide long-acting.
- Section 7.1.5 Discontinuation of study treatment: Added language to provide instruction to investigators on patient discontinuation and corrected the reporting period for safety events after the patients last dose of medication is 30 days for patients on pasiroetide s.c and 84 days for patients on pasireotide long-acting.
- Section 7.1.5.1 Criteria for premature withdrawal: Added language confirming that when current treatment becomes commercially available and reimbursed in the indication, the patient will have to be withdrawn from the study and will have completed the treatment duration from the trial.
- Section 7.1.5.1 Criteria for premature patient withdrawal: Clarified that routine examination is standard of care.
- Section 7.1.7 Follow up for safety evaluations: The language was updated to state that patient must have safety evaluations 84 days after the last dose of study treatment for the pasireotide long-acting and 1 month (30 days) after s.c. dose.
- Section 7.2.2 Safety and Tolerability Assessments: Language added to clarify that investigators can perform safety assessments using their local laboratories as needed per investigator judgement.
- Section 8.2.2 Reporting: The section was updated to replace Drug Safety & Epidemiology (DS&E) with Chief Medical Office & Patient Safety (CMO&PS). The safety reporting language was updated to state that patient must have safety evaluations 84 days after the last dose of study treatment for the LAR and 1 month (30 days) after s.c. dose.
- Section 8.4 Pregnancies: The section was updated to replace Drug Safety & Epidemiology (DS&E) with Chief Medical Office & Patient Safety (CMO&PS)
- Section 10.5.3.1 Analysis set and grouping for analyses: Clarify the duration of the safety follow-up period between s.c. formulation and LAR formulation.
- Section 10.6 Interim Analysis: Added language that an interim analysis will be performed in 2017 and every 2 years thereafter until the final database lock.
- Appendix 1 Medication known to be associated with QT interval prolongation: Removed the list of drugs with possible association with QT prolongation and added the website where the current list of medications can be located.
- Appendix 2 Hepatic safety management: Updated the title to indicate this is a recommended guidance for hepatic management and clarified that routine examination is standard of care.
- Appendix 3 Recommended follow-up in case of QT-related findings during routine ECG: Clarified this is recommended guidance.

- Figure 14-2: Updated title to indicate this is recommended guidance for ECG follow-up.
- Appendix 4 Fasting blood glucose management: Clarified this is recommended guidance.
- Figure 14-3: Updated title to indicate this is a recommended guidance for fasting self-monitoring blood glucose management.
- Appendix 5: Updated the title to reflect this is the dose modification information for patients from the parent protocol CSOM230C2110, CSOM230C2305, CSOM230C2402 and CSOM230C2413.

IRBs/IECs

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.

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 protocol amendment.

Amendment 01

Amendment rationale

With this amendment, in order to clarify the main objective of this study, the previous secondary objective "To collect long-term data on serious adverse events and adverse events of special interest" has been elevated to primary objective. In addition, the protocol has been amended to clarify the safety monitoring guidance and to include the collection of all AEs (including non-serious AEs) and an investigator attestation of continued clinical benefit.

The study continues to allow continued access to pasireotide for patients treated with the compound in previous Novartis sponsored studies for as long as they benefit from it. This roll-over study has been opened since 10-Jun-2013 currently with a total of 95 patients enrolled and 80 patients ongoing.

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 following changes have been implemented:

The Protocol summary is also updated correspondingly

Section 2.1: Update to the study rationale to include the primary endpoint to evaluate long term safety date.

Section 2.6: The inclusion of the Risk-Benefit section

Table 3-1: Updated with revised study objectives and endpoints. The primary objective is to evaluate long term safety data. The secondary objective is to evaluate clinical benefit as assessed by the investigator.

Section 4.1: Updated to clarify that all adverse events and serious adverse events will be collected continuously throughout the study and to specify that at every visit, the investigator is required to confirm that the patient continues to have clinical benefit and may continue receiving study treatment.

Section 6.1.5: Updated to specify that at every visit, the investigator is required to confirm that the patient continues to have clinical benefit and may continue receiving study treatment

Section 6.2: Revised to refer to Appendices regarding dose modification guidelines

Section 6.5: Clarification of drug labeling process

Table 7-1: Updated to include collection of relevant medical history, continuous collection of all AEs and SAEs, investigator confirmation of clinical benefit from study treatment at every visit, the collection of all adverse events and clarification of the visits for LAR and S.C. formulation for the duration of the trial. Also to include the at home monthly pregnancy tests monitoring

Section 7.1.3: Updated to specify that the investigator is required to confirm that the patient continues to have clinical benefit at every visit and may continue receiving study treatment.

Section 7.1.4: Inclusion of Pregnancy and Assessment of Fertility. Also revised language for highly effective contraception.

Section 7.1.5.1: Minor updates to the criteria for premature patient withdrawal from the trial

Section 7.2.2: Update to clarify the safety monitoring guidelines

Section 8: Updated with new AE/SAE reporting process.

Section 9: Clarification to personal identifiable patient information collection

Section 10: Updated statistical analysis section based on revised study objectives.

Section 14: Update to Appendences to reflect revised standard global language for the recommended safety assessments and dose modification

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 Health Authority and IRB/IEC approval prior to implementation.

Protocol summary:

Protocol number	CSOM230B2412
Title	An open label, multi-center pasireotide roll-over protocol for patients who have completed a previous Novartis-sponsored pasireotide study and are judged by the investigator to benefit from continued pasireotide treatment
Brief title	Study to allow access to pasireotide for patients benefiting from pasireotide treatment in a Novartis-sponsored study.
Sponsor and Clinical Phase	Recordati-IV
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to evaluate long term safety data and allow continued use of pasireotide in patients who are on pasireotide treatment in a Novartis-sponsored study and are benefiting from the treatment as judged by the investigator.
Primary Objective(s)	To evaluate long term safety data, SAEs and AEs
Secondary Objective	To evaluate clinical benefit as assessed by the investigator
Study design	This is a multi-center, open label, phase IV study to provide continued supply of pasireotide to patients being treated in a current Novartis-sponsored study and who are benefiting from treatment with pasireotide. Eligible patients are to be consented and can then continue treatment with pasireotide in this protocol. All patients at their scheduled visits will have drug dispensing information and reported adverse events and serious adverse events collected. A patient will reach the end of study when pasireotide treatment is permanently discontinued and the end of treatment visit has been performed. All patients must be followed up for safety evaluations for 84 days following the last dose of pasireotide long acting release (LAR) treatment and for 1 month 30 days following the last dose of pasireotide subcutaneous (s.c.) treatment. The study is expected to remain open for approximately 10 years from First Patient First Visit (FPFV) (or until 10June2023 in the UK). Patients will continue to be treated in this study until they are no longer benefiting from their pasireotide treatment as judged by the Investigator or until one of the protocol discontinuation criteria is met.
Population	Patients who are currently enrolled in a Novartis-sponsored study, that has fulfilled all required assessments and who are benefiting from treatment with pasireotide. Parent studies eligible to participate in the roll-over study will be decided by Recordati
Inclusion criteria	• Patient is currently enrolled in a Novartis- sponsored study receiving pasireotide and has fulfilled all their requirements in the parent study. Patient is currently benefiting from the treatment with pasireotide, as determined by the investigator. • Patient has demonstrated compliance, as assessed by the investigator, with the parent study requirements.
Exclusion criteria	Patient has been permanently discontinued from pasireotide study treatment in the parent study due to unacceptable toxicity, non-compliance to study procedures, withdrawal of consent or any other reason.
Investigational and reference therapy	Pasireotide s.c: should follow parent study doses Pasireotide LAR: should follow parent study doses Combination therapy as per parent protocol
Efficacy assessments	Not applicable
Safety assessments	All adverse events and serious adverse events will be collected continuously throughout the study. Safety monitoring should follow the guidance in the locally approved prescribing information (for locally approved indications) or the requirements described in the current Investigator Brochure (for indications that are not yet approved locally). Additional guidance is provided in the appendices.

Other assessments	Not applicable
Data analysis	The assessment of safety will be based mainly on the frequency and severity of AEs and SAEs. Proportion of patients with clinical benefit as assessed by the investigator will be summarized at scheduled visits. Safety information on patients from this protocol will link to the patient identifiers from the parent study.
Key words	SOM230, pasireotide, roll-over study, pasireotide LAR

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

1.1.1 Overview of Cushing's disease (CD)

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

The most common pathological finding in these patients is bilateral hyperplasia of the adrenal cortex and cortisol hypersecretion due to excessive ACTH secretion. The primary clinical signs and symptoms of Cushing's disease are due to hypercortisolism, such as change in body habitus, hirsutism, wasting of musculature, hypertension, weight gain, and decreased insulin sensitivity with disorders in glucose metabolism, Because of these alterations patients with Cushing's disease have increased morbidity and mortality.

While surgical removal of the adenoma is first line therapy for CD, the success rate of surgery is between 65-90% for microadenomas (tumors < 1 cm) with recurrence rates between 10 to 20% after 10 years. The surgical cure rate for macroadenomas (>1 cm) is less than 65% and recurrence rates as high as 45% (Biller et al 2008). When surgery and/or irradiation fail, or for those patients for whom such therapies are not an option, the remaining alternatives are pharmacological treatment or bilateral adrenalectomy. No drugs are currently approved for the treatment of Cushing's disease and the ones which physicians have available for use are fraught with suboptimal results and significant side effects (Miller 1993, Nieman 2002, Biller et al 2008) and the majority are limited to inhibit steroidogenesis at the adrenals, not targeting the pituitary adenoma. Bilateral adrenalectomy is a definite cure of Cushing's disease but results in irreversible primary adrenal insufficiency and patients need lifelong replacement therapy with glucocorticoids and mineralocotricoids and have a higher likelihood to develop Nelson's syndrome (Sonino 1996, Assie 2004, Assie 2007). There is an unmet medical need for the treatment of CD as medical treatment options are limited.

A confirmatory Phase 3 study [SOM230B2305] has been completed to support the filing of pasireotide s.c. for the treatment of patients with Cushing's disease for whom medical therapy is appropriate. The 900 µg b.i.d group met the pre-specified criteria for the primary efficacy endpoint. Robust reductions in mUFC occurred relatively quickly, within the first month, and were sustained over the course of Months 6 and 12. Both doses were efficacious in lowering mUFC, with the Month 6 median percent change from baseline being -47.9% for both doses. The Month 12 median percent changes from baseline were -62.4% and -67.6% for 900 and 600 µg b.i.d., respectively. Pasireotide s.c. received approval in EU in April 2012 for the treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed.

1.1.2 Overview of acromegaly

Acromegaly is a rare, seriously debilitating condition characterized by chronic hypersecretion of (GH) growth hormone, which, in over 95% of patients, is caused by a GH-secreting pituitary adenoma. It is estimated that about 3 out of every million people develop acromegaly each year and that 40 to 60 out of every million people suffer from the disease at any one time (Melmed et al 1998).

The clinical manifestations of acromegaly are due to the peripheral actions of the GH excess and elevated insulin-like growth factor 1 (IGF-1) concentrations and/or local tumor mass effect. The symptoms and signs of acromegaly can be divided into 3 categories: physical changes due to excessive amounts of GH and IGF-1, metabolic effects of excessive amounts of GH, and local effects of the pituitary tumor (Becker et al 2000).

The therapeutic goals in acromegaly are to reduce mortality to the expected age and sex adjusted rates by using treatments that remove the tumor mass or control its growth and restore GH secretion and action to normal. The biochemical goals of therapy are to reduce the circulating IGF-1 levels to normal for age and sex and to reduce serum GH concentrations to < 2.5µg/L (mean GH concentration of a 5-point profile within a 2-hour time period) or to less than 1µg/L after an oral glucose load (Giustina et al 2000).

A multicenter, randomized, double-blinded, phase III, study [SOM230C2305] completed its core phase and the first year of the extension phase, and patients receiving pasireotide LAR are still being followed. This pivotal study compared the safety and efficacy of 40 mg of pasireotide LAR with 20 mg of octreotide LAR in patients with active acromegaly at 12 months of treatment. The primary objective was to compare the proportion of patients with a reduction of mean GH level to < 2.5µg/L and normalization of IGF-1 to within normal limits (age and sex related) between the two treatment groups at 12 months. The study met its primary endpoint, showing superiority of pasireotide versus octreotide.

1.1.3 Overview of neuroendocrine tumors (NETs)

Neuroendocrine tumors (NETs) are a genetically diverse group of rare malignant tumors that arise from neuroendocrine cells throughout the body. The WHO classification of NETs has recently gained acceptance in the literature due to better prognostic relevance. In this anatomic nomenclature, neuroendocrine tumors are distinguished on the basis of primary tumor localization (e.g. gastrointestinal, lung, or pancreas), rather than the previous embryonic categories (Kloppel et al 2004).

The incidence of NETs is approximately 2 per 100,000 per year. However, NETs has been reported with increasing frequency over the years from 1973 to 2004 (Yao et al 2008).

NETs can be clinically symptomatic (functional) due to hormone or other product hypersecretion or clinically silent (nonfunctional). Approximately 50-60% of NETs are nonfunctional, i.e. do not cause clinical symptoms due to hypersecretion (Modlin et al 2008).

Most patients with NETs present with metastatic disease at the time of diagnosis, with regional or distant metastasis seen in 50% of patients (Yao et al 2008). Up to 75% of patients that present with NETs of the mid- or hindgut region, and approximately 60% of patients with pancreatic NETs (pNET) have liver metastases (Falconi et al 2006).

Currently, surgical resection represents the traditional first-line therapy of NETs (Plöckinger and Wiedenmann 2007). The prognosis following complete surgical resection is generally favorable (Schurr et al 2007). However, curative surgery is often not possible because the majority of patients present with metastatic disease.

In patients with inoperable NET, the treatment goal is to control tumor growth, to control symptoms if the tumor is functional, and to prolong survival time. Biotherapy with currently approved somatostatin analogs (SSAs) remains the mainstay of symptomatic therapy for NET. The PROMID study has shown that octreotide LAR was able to increase time to progression (TTP) when compared to placebo from 6.0 months to 14.3 months in patients with advanced (unresectable or metastatic) NET of the midgut or unknown primary tumor location (Rinke et al 2009). Other available treatment options for patients with NETs are: Interferon-alpha (Öberg 2000, Arnold 2005); cytotoxic chemotherapy as single-agent or in combination (5FU, streptozotocine, doxorubicin, cisplatin, etc.) (Toumpanakis 2007); temozolomide (Ekeblad 2007). For patients with PNET, two new therapies were approved by the FDA in May 2011: everolimus an mTOR inhibitor and sunitinib which is a multikinase inhibitor. Pasireotide s.c. and LAR were evaluated in patients with NETs in two phase 1 [SOM230D2201] and [SOM230C2110] (patients with carcinoid syndrome), one phase 2 [SOM230D2203] (gastrinomas, glucagonomas, insulinomas, VIPomas) and one phase 3 [SOM230C2303] (metastatic functioning carcinoid tumors) studies. The optimal anti-proliferative dose for pasireotide LAR monotherapy in NET is currently being explored in the MTD study [SOM230D2101].

1.1.4 Overview of other pituitary tumors and of Ectopic ACTH secreting (EAS) tumors

Pituitary adenomas are benign neoplasms arising from one of the five anterior pituitary cell types. The clinical and hormonal syndrome associated with pituitary adenomas depend on the cell type from which they are derived. Tumors arising from lactotrope (PRL), somatotrope (GH), corticotrope (ACTH), thyrotrope (TSH), or gonadotrope (LH, FSH) cells hypersecrete their respective hormones. About one-third of all pituitary adenomas are clinically non-functioning (nonfunctional pituitary adenomas, NFPA) and produce no distinct clinical hypersecretory syndrome. Nelson's syndrome is associated with local corticotroph (ACTH) pituitary tumor re-growth, extension or invasion, following a therapeutic bilateral adrenalectomy to control hypercortisolism, as a result of the removal of the negative feedback or cortisol on hypothalamic corticotropin-releasing hormone. Symptoms result from local tumor expansion, and from effects on other pituitary hormones and on ACTH related symptoms.

Hypersectretion of ACTH can also occur from non-pituitary tumors and is designated as Ectopic ACTH secreting (EAS) tumors. The majority of these patients have non-resectable, advanced or metastatic tumors. Symptoms are related to hypersecretion and tumor burden or mass. Prognosis is usually very poor.

Medical therapy is the main measure to alleviate the symptoms of the above diseases by controlling hyper-secretion of respective hormones. Somatostatin analogues are currently used as a medical therapy option in some of these patients. A phase 2 proof of concept study SOM230D2203 is ongoing evaluating the effect of pasireotide LAR in these tumors.

1.1.5 Overview of patients with dumping syndrome

"Dumping syndrome" is a debilitating complication of esophageal and gastric surgeries (such as bariatric and gastric cancer surgeries) estimated to occur in 5-50% of patients (Arts et al 2009). In summary, dumping syndrome consists of (1) a too rapid gastric emptying, (2) an inappropriate release of GI hormones (as a reaction to the rapid delivery of carbohydrates to the duodenum) and (3) a hyperinsulinemic response to a too rapid absorption of glucose. (Tack et al 2009). The diagnosis is confirmed by an adapted 3-hour Oral Glucose Tolerance Test (OGTT) with 75g of glucose evaluating the presence of early changes (30 min) in hematocrit and pulse rate and late (120, 180 min) hypoglycemia (Tack et al 2009).

Currently there are no approved medications to treat dumping syndrome. Dietary measures and addition of food additives such as guar gum and pectin are implemented to prevent late dumping symptoms (Arts et al 2009), (Andersen et al 1989), (Hariu and Lami 1983). Medications that delay carbohydrate absorption such as alpha-glucosidase inhibitors (e.g. acarbose) have been used in clinical practice. However, acarbose improves only the symptoms of late dumping and often results in bloating, flatulence or diarrhea that usually hampers treatment compliance (Lyons et al 1985).

In addition, a relative large body of literature (Arts et al 2009), (Tack et al 2009) (Hopman et al 1988), (Primrose and Johnston 1989), (Tulassay et al 1989) (Geer et al 1990), (Richards et al 1990), (Gray et al 1991) and (Hasler et al 1996) suggests that octreotide (both s.c. and LAR formulations) may be effective.

Clinical studies in healthy volunteers [CSOM230B2216] have demonstrated that pasireotide suppresses insulin secretion, with no changes in hepatic or peripheral insulin sensitivity. In addition, pasireotide significantly decreases incretin response (glugagon-like peptide-1) [GLP-1] and (glucose-dependent insulinotropic peptide) [GIP] right after glucose ingestion during the OGTT until 90- 120 minutes CSOM230B2216. Since it has been shown that the somatostatin inhibition of GLP-1 secretion is mediated by Somatostatin-28 mainly through activation of sst5 and with a lesser effect by sst2 (Chisholm and Greenberg 2002), this suppression is expected to be stronger with pasireotide than with octreotide. A phase 2 study [CSOM230X2203] is ongoing to evaluate the effect of pasireotide s.c. and LAR in patients with dumping syndrome.

1.1.6 Overview of other indications

Pasireotide s.c. and LAR are being studied in several other indications e.g: metastatic prostate cancer [SOM230DE04], metastatic melanoma negative for bRAF and nRAS mutations [SOM230X2404], polycystic liver/renal disease and in post-operative pancreatic fistula.

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

1.2.1 Overview of pasireotide s.c. and LAR

Pasireotide is a cyclohexapeptide somatostatin analogue that exhibits a unique binding profile, binding with high affinity to four of the five known human somatostatin receptors subtypes. Somatostatin analogs 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 tumors, especially in neuroendocrine tumors (Oberg et al 2004), and also in pituitary tumors where hormones are excessively secreted, e.g. in acromegaly (Freda 2002) and Cushing's disease (Van der Hoek et al 2005). Compared to Sandostatin® (octreotide acetate), pasireotide exhibits a binding affinity which is 30-40 times higher for human sst1 and sst5, 5 times higher for human sst3, and a comparable affinity (a 2.5 fold lower) for sst2 receptors.

Pasireotide s.c. is a short acting formulation administered subcutaneously two or three times a day. This formulation has been tested in healthy volunteers and in patients with acromegaly, Cushing's disease and metastatic carcinoid tumors.

Pasireotide LAR is a long acting formulation administered intramuscularly every 28 days. It has been studied in healthy volunteers and in patients with acromegaly, Cushing's disease, and metastatic carcinoid tumors.

1.2.1.1 Non-clinical experience

Pre-clinical pharmacology data on binding affinity and functional activity in vitro and efficacy on hormone secretion in vivo have been obtained with the s.c. formulation in rats, dogs, mice and monkeys.

Extensive safety studies have been performed in mice, rats, rabbits and monkeys to support the administration of pasireotide. These studies include acute, subchronic and chronic toxicity studies, carcinogenicity studies of transgenic mice, local tolerance studies, reproduction studies, as well as *in vitro* and *in vivo* genotoxicity studies. Most of these studies were performed using the s.c. route of administration and the vast majority of the findings were considered related to the pharmacology of pasireotide.

Pre-clinical long-term systemic safety profiles have been well-established for pasireotide s.c. The pre-clinical data from pharmacology, safety, and DMPK studies provided the basis for clinical development of pasireotide s.c.

A detailed summary of available pre-clinical data is provided in the latest version of the pasireotide [Investigator's Brochure].

1.2.1.2 Clinical experience

1.2.1.2.1 Clinical efficacy of pasireotide s.c. and LAR

Pasireotide s.c.

The pasireotide s.c. formulation has shown efficacy in a Phase III Study [CSOM230B2305] in 162 patients with moderate to severe Cushing's disease (CD). In addition, pasireotide s.c. was also evaluated in three phase II studies, two in patients with CD [CSOM230B2208], [CSOM230B2208E], two in patients with acromegaly [CSOM230B2201], [CSOM230B2201E] and one with patients metastatic carcinoid tumors [CSOM230B2202].

A detailed summary of available clinical efficacy data is provided in the [Investigator Brochure].

Pasireotide LAR

Pasireotide LAR formulation has shown efficacy in a randomized placebo-controlled Phase 3 study [SOM230C2305] designed to compare pasireotide LAR to octreotide LAR in patients with acromegaly. A phase III study (CSOM230G2304) has demonstrated that Pasireotide LAR normalized mUFC concentration in about 40% of patients with Cushing's disease at month 7 and had a similar safety profile to that of twice-daily subcutaneous pasireotide. Results of another clinical study have indicated that pasireotide is a safe and effective treatment in patients with acromegaly. Efficacy of pasireotide in patients not controlled with other somatostatin analogues was already demonstrated in the PAOLA study (Study CSOM230C2402). This trial was a double blinded controlled study, in which patients randomized to the active control (octreotide LAR 30mg or lanreotide ATG 120mg) did not achieve biochemical control with further treatment, whereas patients randomly allocated to pasireotide LAR 40 mg or 60 mg were able to achieve biochemical control for the very first time [at 24 weeks, 10 (15%) patients in the pasireotide 40 mg group and 13 (20%) patients in the pasireotide 60 mg group]. Therefore, it is thought that an earlier treatment change to pasireotide LAR might be beneficial for these patients.

1.2.1.2.2 Clinical safety of pasireotide s.c. and LAR

Pasireotide s.c.

Single and multiple doses of pasireotide s.c. have generally been well tolerated by healthy volunteers. The most commonly reported adverse events (AEs) were GI related such as mild diarrhea and nausea, requiring no treatment or study discontinuation. The frequency of these AEs appeared to decrease overtime in multiple-dose studies.

Hyperglycemia was the most important side effect and was observed across all indications. Blood glucose tended to rise with increasing dose, and appeared to be more notable in patients who had a history of hyperglycemia or diabetes mellitus prior to receiving pasireotide. However, hyperglycemia in these patients was responsive to appropriate diabetic management such as adjustments in oral antidiabetic treatment, or in some cases the addition of insulin.

Pasireotide's effect on QT prolongation was demonstrated by two thorough QT (TQT) studies [SOM230B2113] and [SOM230B2125]. The second TQT study SOM230B2125 was designed to evaluate the effect of pasireotide on cardiac intervals using an individualized correction method to account for the known bradycardic effect of pasireotide. It was conducted as a follow-up to Study SOM230B2113, which showed that pasireotide at the Maximum Tolerated Dose (MTD) of 1950 µg b.i.d dose induced prolongation of QTcF, whereas no relevant effect on QTcB was observed. The second TQT study confirmed an effect of pasireotide on QTcI of pasireotide at both the 600 µg bid and the 1950 µg bid dose. The maximal placebo-subtracted change from baseline in QTcI was seen at 2 hours post dose, at which time the mean (90% CI) difference was 13.19 ms (11.38; 15.01) for pasireotide 600 µg bid, and 16.12 ms (14.30; 17.95) for pasireotide 1950 µg b.i.d. Both pasireotide doses decreased heart rate, with a maximal difference to placebo observed at 1 hour for pasireotide 600 µg b.i.d (-10.39 bpm), and at 0.5 hours for pasireotide 1950 µg bid (-14.91 bpm). There were no subjects with QTcI or QTcF values that were increased more than 60 ms from baseline, or that exceeded 500 ms on Day 5, the last day of study treatment.

Three healthy volunteers who received pasireotide s.c. had biochemical changes that met Hy's Law criteria (i.e. ALT > 3 x ULN with concurrent total bilirubin >2 x ULN, without increases in alkaline phosphatase and no other cause(s) identified for the abnormal findings). All 3 cases were asymptomatic, presented within 7 days after initial pasireotide s.c. administration, and were reversible after discontinuation of pasireotide. None of the cases were reported as an adverse event and the subjects completed the respective studies per protocol.

One patient with Cushing's disease fulfilled biochemical criteria for Hy's Law nine days after receiving pasireotide 600 µg b.i.d. Study medication was discontinued due to the event and fourteen days after the discontinuation of pasireotide the patient's bilirubin decreased to 1.6xULN) and ALT was still elevated at 5.8-fold. Liver chemistry tests were normal 45 days after the discontinuation of pasireotide. Follow-up information indicated that liver function tests were consistent with hepatitis.

Pasireotide LAR

Pasireotide LAR has been well tolerated by healthy volunteers and by patients. In healthy volunteers, pasireotide LAR has been well tolerated following single i.m. injection up to the highest tested dose of 60 mg LAR [CSOM230C2101]. The most common adverse events were gastrointestinal. Diarrhea was experienced by most of the subjects and was sometimes associated with flatulence and abdominal pain. The gastrointestinal events were mild or moderate in severity. Mild injection site pain was reported and typically resolved within a day. These events did not result in discontinuation from the study.

Pasireotide LAR formulation has also been evaluated in a randomized phase 3 study in patients with acromegaly [SOM230C2305]. In the pasireotide group, the highest proportion of study drug-related AEs was reported for hyperglycemia-related AEs (58.4%), followed by gallbladder and biliary-related AEs (34.8%) diarrhea-related AEs (33.1%), bradycardia-related AEs (11.2%), pancreatitis-related AEs (11.2%) and nausea-related AEs (10. 1%). Overall the adverse events were similar in both arms with the exception of hyperglycemia, which was found to be more frequent in the pasireotide LAR arm.

The safety and efficacy of Pasireotide LAR was confirmed in a phase 3, multicenter, 12-month trial in which 150 patients were randomized to receive either Pasireotide 10 mg or 30 mg [SOM230G2304]. The most common adverse events were hyperglycaemia (36 [49%] in the 10 mg group and 36 [47%] in the 30 mg group), diarrhoea (26 [35%] and 33 [43%]), cholelithiasis (15 [20%] and 34 [45%]), diabetes mellitus (14 [19%] and 18 [24%]), and nausea (15 [20%] and 16 [21%]). The observed safety profile of long-acting pasireotide was consistent with that of twice-daily pasireotide in patients with Cushing's disease.

Further details on pasireotide clinical safety can be found in the [Investigator Brochure].

1.2.1.2.3 Clinical pharmaokinetics of pasireotide

Pasireotide s.c

In healthy volunteers, results from the human ADME study [CSOM230B2112] with a single s.c. dose of 600 µg ^{14}C-labelled pasireotide showed that pasireotide is mainly eliminated via

hepatic clearance, and renal clearance makes a small contribution to the elimination of pasireotide in man. No circulating metabolite was detected.

In healthy volunteers, following a single s.c. injection, pasireotide pharmacokinetics demonstrated fast absorption, extensive distribution, low clearance, and long half-life [CSOM230B2101], [CSOM230B2106] and [CSOM230C2101]). The PK exposures (Cmax and AUCinf) were approximately dose-proportional for a wide dose range from 2.5 to 1500 µg. The drug was rapidly absorbed with a median Tmax of 0.25-0.5 hr post dose.

Following q.d. dosing of s.c. injections in healthy volunteers, the steady state appeared to be achieved within 3 days [CSOM230B2102]. The CL/F, Tmax, and T1/2 at steady state CSOM230B2102 were similar to those estimated following single doses CSOM230B2101, CSOM230B2106, and CSOM230C2101), indicating that the PK of pasireotide s.c. is linear and time-independent.

Pasireotide LAR

Pasireotide LAR formulation has been evaluated in healthy volunteers, acromegaly patients, and carcinoid patients. Following a single intramuscular (i.m.) injection the LAR formulation demonstrated a controlled-release type of concentration versus time profile with an initial spike phase on day 1 (Cmax,p1), followed by a dip from Days 2 to 7, a second higher peak (Cmax,p2) at approximately day 21, and then a declining phase over the next 6 weeks until the last PK sampling point. PK exposure was dose-proportional for the tested doses 40-60 mg. The relative bioavailability of pasireotide LAR to pasireotide s.c. was complete. PK simulation based on healthy volunteer data demonstrated that steady state could be achieved after 3 monthly injections.

Further details on pasireotide clinical pharmacokinetics can be found in the [Investigator Brochure].

2 Rationale

2.1 Study rationale and purpose

The purpose of this rollover study is to evaluate long term safety data and allow continued supply of pasireotide (s.c. and/or LAR) to patients who are currently receiving treatment in a Novartis-sponsored trial and have fulfilled all required assessments in the parent study, are benefiting from the treatment as judged by the investigator and are unable to access pasireotide treatment outside of a clinical study. Parent studies eligible to participate in the roll-over study will be decided by Recordati. Investigator initiated trials (IITs) will not be included. The patient must have fulfilled all required assessments in the parent study and the parent study must be in the process of being completed or terminated and reported.

Patients will continue to receive pasireotide alone or in combination with another treatment for Cushing's Disease and Acromegaly, as long as they continue to benefit as per Investigator assessment, or until one of the discontinuation criteria is met (please refer to Section 7.1.5).

2.2 Rationale for the study design

This is a multi-center, open label, phase IV, roll-over study of pasireotide in patients being treated in a current Novartis-sponsored study and who are benefiting from treatment with pasireotide alone or in combination with another treatment for Cushing's Disease and Acromegaly. Combination therapy will only be permitted for patients with Cushing's Disease or Acromegaly.

The study will not include a screening phase as patients will transfer directly from parent studies and will commence treatment with pasireotide alone or in combination with another treatment for Cushing's Disease and Acromegaly, as soon as they are consented and meet the inclusion criteria of the roll-over protocol. Since this study is intended to provide pasireotide supply and no formal analysis will be performed, there is no need for randomization, nor for bias reducing measures.

2.3 Rationale for dose and regimen selection

The selected doses and regimen will be based on the dose ranges and regimen available in the parent study. The starting dose of pasireotide alone or in combination with another treatment for Cushing's Disease and Acromegaly, should be the same dose as that which the patient was receiving in the parent study at roll over. After the starting dose, changes to pasireotide dose, and/or any medication given in combination with pasireotide for Cushing's Disease or Acromegaly, will be based on the investigator's judgment, but must follow the dose ranges provided in the parent study. Please note combination treatment in this rollover trial is only allowable for Cushing's Disease and Acromegaly parent protocols.

Pasireotide will be provided as:

1. Pasireotide s.c. – to be administered subcutaneously two or three times a day depending on the parent study dosing.
2. Pasireotide LAR to be administered as intramuscular injection every 28 days.

2.4 Rationale for choice of combination drugs

Patients suffering from Cushing's disease or Acromegaly represent a challenge because of the reduced control of cortisol or GH/IGF-1 levels, respectively, by some medical therapies especially when given as montherapy. Due to this, whilst treatment is being administered, a close follow up is necessary to evaluate a response to the medication while assessing the addition of a second medication.

In some patients, the administration of pasireotide alone did not normalize cortisol levels. Thus, a second medication with another mechanism of action is added to aid the restoration of cortisol or GH/IGF-1 levels to the normal range, respectively.

For subjects on combination treatment with cabergoline + pasireotide only. The treatment of patients with CD requires a multimodality approach. Pasireotide has a favorable benefit/risk profile in Cushing's Disease. However, a main reason for treatment discontinuation is due to insufficient therapeutic effect. Cabergoline is often used to decrease cortisol levels but it presents treatment escapes in many patients. Taking into consideration that biochemical

remission should be rapidly achieved to reverse morbidity and mortality, drugs can be combined to control cortisol production within an acceptable time frame.

Advances in combination medical therapy have opened up new perspectives for acromegaly patients who are poorly controlled, or nonresponsive to presently available single drug therapies. SSAs have a role as the primary medical therapy in patients who have a low likelihood of surgical remission, or who are poor surgical candidates, as adjuvant therapy in these patients with persistently non suppressible GH or elevated IGF-I levels (or both) after pituitary surgery or during the interim period after RT. In patients who do not respond (biochemically) to medical monotherapy, combination therapy with SSAs and cabergoline or pegvisomant and cabergoline can be considered, on the basis of individual clinical considerations including tumour size and location.

2.5 Rationale for choice of comparators drugs

Not applicable.

2.6 Risks and benefits

Acromegaly is a serious, chronic, debilitating disease that is associated with high morbidity, shortened life expectancy, and a reduced quality of life. If untreated, acromegaly is associated with an average 10-year reduction in life expectancy, mainly due to cardiovascular, cerebrovascular, metabolic, and respiratory comorbidities. While successful pituitary surgery leads to long-term biochemical control in more than 70% of patients with well-circumscribed microadenomas, the success rate for macroadenomas is around 50%, and even less for invasive tumors. Radiotherapy is currently mainly used in patients with recurrent or persistent tumors, and carries the disadvantages of a relatively long latency period; furthermore, progressive anterior pituitary insufficiency develops in more than 50% of patients. Medical therapy using SSAs is being increasingly used as first-line treatment, especially in patients with low likelihood of cure by surgery, in whom surgery is contraindicated, or who refuse surgery. The efficacy of pasireotide LAR has been demonstrated to be superior to that of first-generation SSAs both in terms of the probability of a patient achieving biochemical control (GH reduction and normalization of IGF-1 levels), and in terms of relative reduction of IGF-1 levels from baseline. Superiority was demonstrated, both in medically naïve patients and in patients inadequately controlled on prior medical therapy.

Cushing's disease is a very rare, debilitating, and life-threatening disease that is caused by an adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma most commonly affecting adult females. The tumors are usually microadenomas (≤ 1 cm in diameter); macroadenomas are rare. The elevated levels of ACTH secreted by these tumors stimulate the adrenal glands to produce excess cortisol, thereby leading to the subsequent development of the clinical signs and symptoms of hypercortisolism. The primary clinical symptoms of Cushing's disease include the following: changes in body habits due to increased fat accumulation; hirsutism; skin changes with easy bruising, purplish striae, reddening and ulceration of the cheeks; generalized weakness and fatigue; wasting of musculature; menstrual disorders in females; decreased fertility and/or libido; hypertension; weight gain; increased insulin resistance with alterations in glucose metabolism; dyslipidemia; depression, mood and behavior disorders; sleep disturbances and osteopenia/osteoporosis. Moreover, hypercortisolism is also associated with

immune deficiency and an increased risk for infections. As a result, patients with Cushing's disease have increased morbidity and a mortality rate 4 times higher than age- and gender-matched subjects. The initial (i.e. first line) treatment of choice for Cushing's disease is pituitary adenomectomy (transphenoidal surgery). For patients with recurrent or persistent disease, repeat transphenoidal surgery is also recommended if possible, but it is associated with lower efficacy than the initial surgery. Beyond this, radiotherapy and bilateral adrenalectomy are alternative treatment options. All 3 treatment modalities are associated with the potential for serious side effects. Pasireotide is the first pituitary-targeted medical therapy to demonstrate efficacy directly aimed at the underlying mechanism of Cushing's disease (i.e. increased ACTH secretion), with associated robust and sustained decreases in UFC and serum cortisol. Additionally, improvements in the clinical signs and symptoms of Cushing's disease were observed and were associated with decreases in UFC even in patients that did not completely normalize UFC; similar findings were observed for HRQL.

Neuroendocrine tumors (NET) are rare malignant neoplasms that arise from the diffuse neuroendocrine system, which is made up of peptide- and amine producing cells with different hormonal profiles depending on their site of origin. Secretory symptoms of NETs occur when hormonal secretions released by the tumors reach the systemic circulation in a sufficient concentration and escape hepatic degradation; this occurs most frequently with hepatic metastases of NETs. Many NETs of non-pancreatic origin release vasoactive peptides and amines, such as serotonin and tachykinins, into the systemic circulation and cause a characteristic set of symptoms including flushing and diarrhea, and less commonly abdominal pain, telangiectasia, and bronchoconstriction. Depending on the tumor location, 10-50% of patients will have these symptoms. These symptoms occurring collectively are classically referred to as "carcinoid syndrome". Surgical resection of the primary and metastatic lesions, if possible, remains the mainstay of treatment, and the only way to obtain a cure. Surgery is often not possible, however, as NETs are detected frequently in a more advanced tumor stage, regardless of primary location. In addition, approximately 60% of patients will continue to experience symptoms after surgery. In patients with inoperable GI NET, the treatment goal is to control tumor growth, to control any secretory symptoms that may be present, and to prolong survival. Somatostatin analogs (SSA) have been approved worldwide for the control of secretory symptoms of patients with NET for many years, and are widely used for symptom control in GI NETs. Over the past years, prospective data have become available to support the anti-proliferative role of somatostatin analogs. Given the broader binding capacity of pasireotide LAR, it is anticipated that it may have a greater impact on tumor stabilization than other SSAs such that significant benefit can be provided to patients that have progressed on currently available therapies. Evidence of efficacy was obtained in study CSOM230C2303. As there is no current standard of care for patients with advanced progressive functional GI NET, offering patients improved tumor stabilization will satisfy a high unmet need. Pasireotide LAR may provide a next step of therapy upon progression on other SSAs and provide patients an alternative to more toxic regimens such as standard cytotoxic chemotherapy that has limited benefit in this indication. In a post-hoc analysis from study CSOM230C2303, pasireotide LAR was shown to improve progression-free survival (PFS) by 5 months as assessed by investigators, compared to octreotide LAR.

Dumping syndrome is a debilitating complication of esophageal and gastric surgeries (such as bariatric and gastric cancer surgeries) estimated to occur in 5-50% of patients. These surgical

procedures result in a reduced gastric capacity that causes rapid influx of nutrients to the small intestine, inducing a cascade of pathophysiological events and leading to early and late dumping syndrome symptoms. Dumping syndrome consists of (1) a too rapid gastric emptying, (2) an inappropriate release of GI hormones (as a reaction to the rapid delivery of carbohydrates to the duodenum) and (3) a hyperinsulinemic response to a too rapid absorption of glucose. Early symptoms comprise both gastrointestinal and vasomotor symptoms. Late dumping symptoms include hypoglycemia, perspiration, palpitations, hunger, fatigue, confusion, aggression, tremor and syncope. No drugs are currently approved for the treatment of Dumping syndrome. Pasireotide is a potent inhibitor of incretin and insulin secretion (via sst2 and sst5), which prevents postprandial hypoglycaemia. Additionally, it is a more potent inhibitor of glucagon-like-peptide-1 (GLP-1) and peptide YY secretion than octreotide. Results from a phase II study (CSOM230X2203) suggest that pasireotide effectively controls postprandial hypoglycaemia in patients with dumping syndrome and provides improvements in the hematocrit level and pulse rate.

Malignant melanoma (MM) is a highly invasive form of skin cancer that arises via transformation of the normal melanin-producing cells of the epidermis. Clinical outcome is dependent on the extent of disease at diagnosis with excellent survival rates (approximately 90% at 5 years) described for patients with stage I disease. By contrast, patients with unresectable metastatic melanoma (stage III-IV) have a high 5-year mortality rate. Traditional therapies such as conventional chemotherapy (DTIC) and immunotherapies (IFN-α, IL-2) have not improved OS despite responses of short duration or benefit in a small number of patients. Newer therapies, including ipilimumab and vemurafenib, are now considered the standard of care because of their demonstrated survival benefit in patients with metastatic melanoma. Many patients, however, still experience disease progression after treatment, especially those whose melanoma does not express mutations in the BRAF gene (nearly half the overall melanoma patient population). Therefore, the development of new strategies to improve treatment of this life-threatening disease is essential. **Merkel cell carcinoma** (MCC) is a neuroendocrine carcinoma of the skin and hair follicles which often follows a particularly aggressive course. MCC is a rare tumor, accounting for less than 1% of cutaneous malignancies. Overall, the 2-year mortality rate is 30-50%; few studies include a longer-term follow-up. To date, there is no standard protocol for the management of MCC and surgical treatment of large tumors especially in the head and neck region can be disfiguring. There is an urgent need for new therapies to treat patients with MCC. Pasireotide represents a new therapeutic option for patients with metastatic melanoma and Merkel cell carcinoma that has low toxicity and a good safety profile. Preclinical evidence and extensive clinical data and experience from the use of SSAs in patients with other endocrine and cancer disease states support the use of pasireotide in patients with malignant melanoma and Merkel cell carcinoma.

Pasireotide is currently approved for use in Cushing's disease (s.c. formulation) in over 80 countries, and for use in acromegaly (i.m. LAR formulation) in over 30 countries worldwide. The safety profile of both formulations of pasireotide has been well characterized in a comprehensive development program and is similar to the established profile of SSAs, except for the higher incidence and magnitude of hyperglycemia, which is manageable with proper treatment with anti-diabetic medication. The mechanism of the pasireotide-induced hyperglycemia has been well characterized in mechanistic studies. It is primarily a consequence of decreased secretion of insulin and incretins, with no change in hepatic or peripheral insulin

sensitivity, is less severe in responders than non-responders, and is reversible upon discontinuation. The risk of hyperglycemia is minimized by monitoring of patients' FPG and HbA1c levels and appropriate management. Additional expected pharmacodynamic effects of pasireotide are well known and are primarily GI disturbances, bradycardia, mild QT prolongations, cholelithiasis and transient elevations in serum levels of transaminases. These effects can be effectively monitored and managed, as detailed in the IB and in the label. No unexpected new findings have emerged with long-term exposure to pasireotide.

Overall, pasireotide has a favorable benefit/risk profile in the discussed indications. Patients rolled-over to this study are those who have benefited from the treatment with pasireotide and continue to obtain this benefit with continuation of the treatment. The current label and IB fully characterize both efficacy and safety aspects of pasireotide, s.c. and LAR, to enable its appropriate use to maximize benefit while minimizing risks to patients. The risk to patients in this trial may be minimized by compliance with the eligibility criteria and study procedures, and close clinical monitoring. There may be unforeseen risks with pasireotide which could be serious.

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
Primary		
To evaluate long term safety data i.e. SAEs and AEs	Frequency and severity of AEs/SAEs	Refer to Section 10.4
Secondary		
To evaluate clinical benefit as assessed by the investigator.	Proportion of patients with clinical benefit as assessed by the investigator at scheduled visits.	Refer to Section 10.5
Other secondary		
Not applicable	Not applicable	Refer to Section 10.5.2

4 Study design

4.1 Description of study design

Those patients receiving pasireotide LAR must return to the study center monthly (+/- 7 days) to receive study medication. Drug dispensing information will be collected and adverse events and clinical benefit will be assessed. Patients receiving pasireotide s.c. must return to the study center on a quarterly basis (every 12 weeks +/- 2 weeks) for resupply of study medication. Drug dispensing information will be collected and adverse events and clinical benefit will be assessed. The patient may return to the clinic at any given time as per standard of care or treating physician recommendation; however, only the quarterly study visits will be recorded.

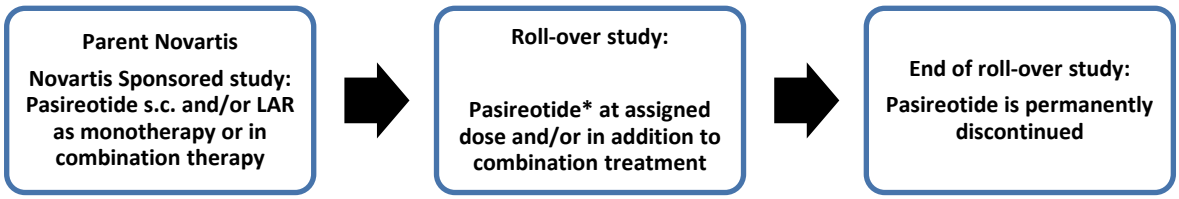
At every visit, the investigator is required to confirm that the patient continues to have clinical benefit and may continue receiving study treatment.

All adverse events and serious adverse events will be collected continuously throughout the study. Information on patient pregnancies and pregnancies of pregnant partners will be collected.

The study is expected to remain open for 10 years from FPFV (or until 10-Jun-2023 in the UK). Patients will continue to be treated in this roll-over study until they are no longer benefiting from their pasireotide treatment as judged by the investigator or until one of the discontinuation criteria is met (please refer to Section 7.1.5). At each visit the Investigator is required to confirm that the patient continues to derive clinical benefit and may continue receiving study treatment.

A patient will reach the end of study when pasireotide treatment is permanently discontinued.

Figure 4-1 Study design



*Note: The starting dose of pasireotide, and any combination treatment given for Cushing's Disease or Acromegaly, should be the same dose as that which the patient was receiving in the parent study at roll over.

4.2 Timing of interim analyses and design adaptations

Interim analyses will occur every 2 years beginning in 2017 and continuing until the final trial database lock.

4.3 Definition of end of the study

End of study is defined as either 10 years from FPFV (or until 10-Jun-2023 in the UK) or when all patients on this study have permanently discontinued pasireotide treatment or have been able to obtain commercial supply according to local regulations or have been able to receive the drug through country-specific programmes outside of this clinical trial (applicable to Brazil, France, Germany, India, Italy, Malaysia, Mexico, Peru and Thailand) and the end of treatment visit and all safety follow-up procedures have been performed for each patient, whichever comes first.

4.4 Early study termination

The study can be terminated at any time for any reason by Recordati. Should this be necessary, the patient should be informed as soon as possible and should stop taking study labeled drug.

Assessments should be performed as described in Section 7.1.3 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 investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.2 Inclusion criteria

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

1. Patient is currently participating in a Novartis-sponsored study receiving pasireotide (LAR and/or s.c.) on monotherapy or combination therapy (for Cushing's Disease or Acromegaly), and has fulfilled all required assessments in the parent study and patients that are benefiting from the study treatment have no other alternatives.
2. Patient is currently benefiting from the treatment with pasireotide, as determined by the investigator
3. Patient has demonstrated compliance, as assessed by the investigator, with the parent study requirements.
4. Willingness and ability to comply with scheduled visits, treatment plans and any other study procedures.
5. Written informed consent obtained prior to enrolling in roll-over study and receiving study medication.
    - If consent cannot be expressed in writing, it must be formally documented and witnessed, ideally via an independent trusted witness.

5.3 Exclusion criteria

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

1. Patient has been permanently discontinued from pasireotide study treatment in the parent study due to unacceptable toxicity, non-compliance to study procedures, withdrawal of consent or any other reason.
2. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
3. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception during the study treatment and for 30 days after the final dose of pasireotide s.c. and 84 days after the final dose of pasireotide LAR. **Highly effective** contraception is defined as either:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the patientt. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male sterilization (at least 6 months prior to enrolling). For female patients on the study the vasectomized male partner should be the sole partner for that patient.
- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
- In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.
- Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child-bearing potential.
- Sexually active males unless they use a condom during intercourse while taking drug and for 1 months after pasireotide s.c. last dose and 3 months after pasireotide LAR last dose and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.

If a study patient or partner becomes pregnant or suspects being pregnant during the study treatment or within 1 month after the final dose of pasireotide s.c. or 84 days after the final dose of pasireotide LAR, the Study Doctor needs to be informed immediately and ongoing study treatment with pasireotide has to be stopped immediately. For patients taking pasireotide LAR, the future dose injections will be cancelled.

6 Treatment

6.1 Study treatment

Terms related to study treatment are defined below:

6.1.1 Study treatment and investigational treatment refer to pasireotide alone or in combination with another treatment for Cushing's Disease and AcromegalyDosing regimen Pasireotide

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
Pasireotide	Subcutaneous	Dose ranges should be the same as stated in the parent study	b.i.d. or t.i.d depending on the parent study guidance
Pasireotide LAR	Intramuscular	Dose ranges should be the same as stated in the parent study	q 28 days

Pasireotide may be provided in two different formulations LAR or s.c. (Table 6-1), depending on the parent study. The starting dose of pasireotide should be the same dose as that which the patient was receiving in the parent study at roll over. Following the starting dose patients may have their dose changed based on investigator's judgment and following the dose ranges used in the parent study. Patients are not allowed to receive doses that are not indicated in the parent study.

The investigational treatment is to be stored in a secure locked area while under the responsibility of the investigator. Receipt and dispensing of investigational treatment must be recorded by an authorized person at the investigator's site.

Pasireotide for the roll-over study can be provided as local commercial material or global clinical study supply as appropriate. As per Recordati procedures, investigational treatment will be shipped directly to the investigational sites.

6.1.2 Dosing regimen for patients on Pasireotide in combination with cabergoline treatment

Cabergoline is in the form of 0.5mg tablet. Cabergoline should be taken according to guidelines in the parent protocol. It is usually taken after a full meal. As per the parent study, if monotherapy with pasireotide does not allow the patient to receive biochemical control, cabergoline can be added at a starting dose of 0.5mg once daily. If the patient does not achieve biochemical control with cabergoline 0.5mg once daily treatment, in combination with pasireotide, then the cabergoline dose can be escalated up to 1.0mg once daily.

Dostinex is a generic form of cabergoline and can be used in the trial. If Dostinex is not available in a participating country, a different type of generic form can be used. For storage conditions, please refer to cabergoline Package Insert and SmPC.

For specific study treatment dose modifications regarding cabergoline in the SOM230B2411 trial, please refer to (appendix 12).

Cabergoline is mainly recommended for patients with borderline or moderately increased plasma IGF-I levels (<1.5 X the upper limit of normal), even though it is sometimes effective (leading to normal IGF-I levels) in patients with high baseline IGF-1 levels. More recent studies suggest that cabergoline, a more selective dopamine-2 receptor agonist, may be effective in a larger percentage of patients by further lowering GH or IGF-1 levels. Doses vary from 0.3 to 7

mg/wk (one to seven administrations per week). The maximum suppression of GH has been achieved from 0.5 mg daily to 1 mg twice weekly.

6.1.3 Dosing regimen for patients on Pasireotide in combination with another treatment for Cushing's Disease or Acromegaly

Please follow all dosing guidelines outlined in the parent protocol for patients on any combination treatments.

6.1.4 Ancillary treatments

Not applicable

6.1.5 Rescue medication

Not applicable

6.1.6 Guidelines for continuation of treatment

Not applicable

6.1.7 Treatment duration

Patients will continue to receive pasiroetide alone or in combination with another treatment for Cushing's Disease and Acromegaly, as long as they continue to derive benefit as per Investigator assessment, the drug becomes commercially available in their country, or until one of the discontinuation criteria is met (please refer to Section 7.1.5). At every visit, the investigator is required to confirm that the patient continues to have clinical benefit and may continue receiving study treatment. A patient will reach the end of the roll-over study when pasireotide treatment is permanently discontinued.

6.2 Dose modification guidelines

The starting dose of pasireotide alone or in combination with another treatment for Cushing's Disease and Acromegaly, should be the same dose as that which the patient was receiving in the parent study at roll over. Changes to pasireotide, and any medication given in combination with pasireotide dose, will be based on the investigator's judgment.

Please refer to Appendix 2 through Appendix 12 (Section 14.2 through Section 14.12) for dose modification guidelines.

6.2.1 Starting dose rationale

The starting dose of pasireotide alone or in combination with another treatment for Cushing's Disease and Acromegaly, should be the same as that which the patient was receiving in the parent study at the roll over.

6.3 Concomitant medications

6.3.1 Prohibited concomitant therapy

The use of concomitant medication with known risk of Torsades de pointes (TdP) is prohibited. In case a patient needs to take a medication with known risk of TdP, it will require study drug discontinuation prior to starting the medication. Please see Appendix 1 for further guidance on QT prolonging medication.

Medications with a potential risk of TdP should be avoided whenever possible.

Refer to Appendix 1 for guidance regarding medications which pose a known risk for QT prolongation.

6.4 Patient numbering, treatment assignment or 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 enrolled in the roll over study 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 Recordati 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 through the Oracle Clinical Remote Data Capture interface. Additionally, an e-CRF will be completed that identifies the patient by gender and data of birth and previous study, site/center and subject number.

6.4.2 Treatment assignment or randomization

Not applicable

6.4.3 Treatment blinding

Not applicable

6.5 Study drug preparation and dispensation

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

Investigator staff will identify the study treatment package(s) to dispense to the patient. Investigator staff will add the patient number on the label. For global supply the study medication packaging has a 2-part label. Immediately before dispensing the package, Investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique patient number.

6.5.1 Study treatment packaging and labeling

Pasireotide for the roll-over study can be provided where appropriate as local commercial material or as global clinical study supply (Open label), packed and labeled under the

responsibility of the Sponsor's Clinical Supply. Study treatment 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.

Combination treatments should be labeled and supplied in accordance with the parent protocol. When available, commercial treatment should be used as a first option.

Table 6-2 Packaging and labeling

Study treatments	Packaging	Labeling (and dosing frequency)
Pasireotide s.c. (0.3mg, 0.6mg and 0.9mg)	Solution for subcutaneous injection in ampoule	Labeled as 'SOM230' (b.i.d. or t.i.d)
Pasireotide LAR (10mg, 20mg, 40mg and 60mg)	Microparticle powder for suspension in vial	Labeled as 'SOM230 LAR' (q28d)
	Solution for suspension (vehicle) in ampoule	Labeled as 'solvent' (q28d)

6.5.2 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, pasireotide alone or in combination with another treatment for Cushing's Disease and Acromegaly, should be stored according to the instructions specified on the drug labels and in the [Investigator's Brochure]. For patients receiving pasireotide s.c., a 3-month supply of pasireotide can be dispensed to the patient. Patients receiving pasireotide LAR, must return monthly to the participating site to receive their injections. During these visits, limited drug dispensing information will be collected and reported within the drug accountability log.

Table 6-3 Supply and storage of study treatments

Study treatments	Supply	Storage
Pasireotide s.c.	local commercial material or global clinical study supply (open label) supplied by Sponsor	Refer to study treatment label
Pasireotide LAR	local commercial material or global clinical study supply (open label) supplied by Sponsor	Refer to study treatment label
Combination treatments	Should be supplied in accordance with the parent protocol. Where available, commercial treatment should be used as a first option.	Refer to study treatment label

6.5.3 Study drug compliance and accountability

6.5.3.1 Study drug 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.

6.5.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. 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 the end of the study or at the time of study treatment discontinuation.

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

6.5.3.3 Handling of other study treatment

Not applicable.

6.5.4 Disposal and destruction

The drug supply can only be destroyed once the study drug accountability check has been performed by the monitor. The study drug supply can be destroyed at the local Recordati facility, by Drug Supply group or by a 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	Protocol Reference Section	Enrollment	Visits during treatment phase	End of study treatment (EoT)	End of study /Safety Follow-up
Visit Number			**1**	**Visit 2,3,4 etc.**	**777**	778
Demographic: Patients' previous study, site, subject number, study dose, formulation and frequency, study indication	D	7.1.2.3	x			
Informed consent	D	5.2/5.3/11.3	x			
Relevant medical history/current medical conditions	D	7.1.2.3	x			
Inclusion/exclusion criteria	D	5.2/5.3	x			
Pasireotide s.c. dispensing (+combined therapy if applicable)	D	6.1	x	x x x x x x x x x x x x		
Pasireotide LAR dose administration (+combined therapy if applicable)	D	6.1	x	x x x x x x x x x x x x		
Pregnancy Tests	D	7.1.4	x	← Monthly (home) →	x	x
Investigator confirmation of continued clinical benefit from study treatment (at every visit)	D	6.1.5	x	**Visit 2,3,4 etc.**		
Serious adverse events (in safety database only)	D	8.2	← Continuous →			x
AEs	D	8.1	← Continuous →			x
End of treatment	D	7.1.5	x		x	
End of study	D	7.1.5				x

7.1.1 Molecular pre-screening

Not applicable.

7.1.2 Screening

There will be no screening period for this study. At the enrollment visit, the patient will need to complete a written informed consent. Once consented, patients will be evaluated for eligibility via the inclusion and exclusion criteria.

7.1.2.1 Eligibility screening

Not applicable.

7.1.2.2 Information to be collected on screening failures

Not applicable.

7.1.2.3 Patient demographics and other baseline characteristics

For patients who are eligible to participate in this roll over study, an e-CRF will be completed that identifies the patients' gender, data of birth and previous study, site /center and subject number. Study dose, formulation and frequency, study indication and relevant medical history will also be collected.

7.1.3 Treatment period

The starting dose of pasireotide, and any medication given in combination with pasireotide, should be the same dose as that which the patient was receiving in the parent study at roll over.

Those patients receiving pasireotide LAR must return to the study center monthly (+/- 7 days) to receive study medication. Drug dispensing information will be collected and adverse events and clinical benefit will be assessed. Patients receiving pasireotide s.c. must return to the study center on a quarterly basis (every 12 weeks +/- 2 weeks) for resupply of study medication. Drug dispensing information will be collected and adverse events and clinical benefit will be assessed. The patient may return to the clinic at any given time as per standard of care or treating physician recommendation; however, only the quarterly study visits will be recorded. The study is expected to remain open for approximately 10 years from FPFV (or until 10-Jun-2023 in the UK) or when all patients on this study have permanently discontinued pasireotide treatment or have been able to obtain commercial supply according to local regulations or have been able to receive the drug through country-specific programmes outside of this clinical trial (applicable to Brazil, France, Germany, India, Italy, Malaysia, Mexico, Peru and Thailand) and the end of treatment visit and all safety follow-up procedures have been performed for each patient, whichever comes first. At every visit, the investigator is required to confirm that the patient continues to have clinical benefit and may continue receiving study treatment.

7.1.4 Pregnancy and assessment of fertility

Since highly effective contraception is required during the study, female patients of child bearing potential are required to test negative for a pregnancy (either with serum testing if routinely/locally available or urine pregnancy test) before enrolling into the study.

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception during the study and for 30 days after the final dose of pasireotide s.c. and 84 days after the final dose of pasireotide LAR.

Highly effective contraception is defined as either:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male sterilization (at least 6 months prior to enrolling). For female patients on the study the vasectomized male partner should be the sole partner for that patient.
- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

If patient has tested negative at the end of study on the parent study, no pregnancy testing is required if enrollment into this study is carried out on the same day or within a maximum of 5 days from each other.

Female patients of child bearing potential are required to perform monthly home urine pregnancy tests and complete a simple diary with the dates and the outcome of the home urinary test while on study treatment and during safety follow-up (30 days after the final dose of pasireotide s.c. and 84 days after the final dose of pasireotide LAR).

A pregnancy test (either with serum testing if routinely/locally available or urine pregnancy test) on female patients of child bearing potential is required at the final study visit.

Any positive results will be recorded in the database and followed up as per Section 8.4.

7.1.5 Discontinuation of study treatment

Patient may voluntarily discontinue from the study treatment for any reason at any time. If a patient decides to discontinue from the study treatment, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information in the patient's chart and on the appropriate CRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reasons.

At the time the patient discontinues study treatment, a visit should be scheduled as soon as possible, at which time the assessments listed for the End of Treatment (EOT) visit will be performed. End of Treatment information will be completed in the eCRF giving the date and reason for stopping the study treatment (see Section 7.1.5.1).

At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations 1 month following last dose of the s.c. dose or 3 months for patients receiving LAR, following last dose. The completion of the Study Evaluation Completion CRF page will be required any time a patient discontinues from the study and must be completed 30 days after the end of treatment.

7.1.5.1 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 may be withdrawn from the study if any of the following occur:

- Death.
- Lost to follow-up.
- Staying in the study would be harmful.
- Patient/guardian decision.
- Physician decision.
- Non-compliance to protocol requirements.
- Protocol deviation.
- Pregnancy.
- Study terminated by sponsor.
- Study treatment has become available through country-specific programmes outside of this clinical trial (applicable to Brazil, France, Germany, India, Italy, Malaysia, Mexico, Peru and Thailand).

Study treatment has become commercially available and reimbursed (when current treatment becomes commercially available and reimbursed in that indication, the patient will have to be withdrawn from the study and will have completed the study as per protocol).

In addition to the general withdrawal criteria, the following criteria may also require study treatment discontinuation:

If any of the criteria below are met during routine examinations that are part of standard of care, study medication should be discontinued immediately. Re-challenge of study medication is prohibited once discontinuation criteria are met.

Hepatic-related discontinuation criteria

- Jaundice or other signs of clinically significant liver dysfunction
- ALT or AST > 3 x ULN and Total Bilirubin ≥ 2 x ULN and ALP < 2 x ULN
- ALT or AST > 5 x ULN and ≤ 8 x ULN persistent for more than 2 weeks
- ALT or AST > 8 x ULN

QT related discontinuation criteria

- Confirmed QTcF >500 ms and discontinuation recommended by a cardiologist
- QTcF > 480 msec, if the investigator determines it is no longer safe for the patient to continue in the study, based on ECGs, cardiac examination and recommendation from a cardiologist.
- Clinically significant arrhythmias including:
  1. Any ventricular or supra-ventricular tachyarrhythmia associated with symptoms of hemodynamic compromise.
  2. Sustained ventricular tachycardia (>30 s) irrespective of symptoms.
  3. Recurrent non-sustained VT (≥ 3 beats) during any 24-hour monitoring period.
  4. Clinically significant brady-arrhythmia or third degree AV block.
  5. Need to use a drug with known risk of TdP.

Hyperglycemia related discontinuation criteria

- Uncontrolled diabetes mellitus (DM), consistently high glucose values FPG ≥ 240 mg/dL (13.3 mmol/L) or HbA1c value ≥ 10 % despite appropriate management of diabetes including diet and/or exercise with or without optimal anti-diabetic therapy

7.1.5.2 Replacement policy

Not applicable.

7.1.6 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact.

Recordati will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be retained and analyzed at a later date (or as required by local regulations).

If a patient withdraws consent, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information.

Study treatment must be discontinued and no further assessments conducted.

Further attempts to contact the patient are not allowed unless safety findings require communication or follow up.

7.1.7 Follow up for safety evaluations

All patients must have safety evaluations 84 days after the last dose of study treatment for the LAR and 1 month (30 days) after s.c. dose.

Patients lost to follow up should be recorded as such on the eCRF. 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.

Data collected should be added to the Adverse Events eCRF.

7.1.8 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow up should be recorded as such on the appropriate Disposition CRF.

7.2 Assessment types

7.2.1 Efficacy assessments

Not applicable.

7.2.2 Safety and tolerability assessments

Safety will be monitored by collecting adverse events/serious adverse events at every visit. For details on AE/SAE collection and reporting, refer to Section 8.

In addition, the following applies for safety monitoring:

- For locally approved indications, the safety monitoring guidance in the locally approved prescribing information applies
- For indications that are not yet approved locally, the safety monitoring requirements described in Section 7.2 of the current Investigator Brochure must be followed

Patients may have safety assessments performed by the clinics local laboratory as per investigators judgement and standard of care at any time during the study period.

7.2.2.1 Hepatic related findings

For any hepatic related findings during routine follow up, refer to Appendix 2.

7.2.2.2 QT-related finding

For any QT-related finding during routine follow up, refer to Appendix 3.

7.2.2.3 Hyperglycemia related findings

For any hyperglycemia related finding during routine follow up, refer to Appendix 4.

7.2.2.4 Additional bio-marker assessments

Not applicable.

7.2.3 Resource utilization

Not applicable.

7.2.4 Patient reported outcomes

Not applicable.

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).

Any ongoing adverse events from the parent study will be captured as medical history in the roll-over database. Any AE that begins (or worsens) after signing of the informed consent for the roll-over and during the 30-day (or 28-day) or 84-day (12 week) safety follow up period defined in the parent protocol should be reported in both clinical databases.

Adverse event monitoring should be continued for at least 30 days for patients receiving the s.c. formulation and 84 days for those receiving the LAR formulation (or 5 half-lives), whichever is longer) 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 current version of Common Terminology Criteria for Adverse Events (CTCAE).

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected through the EOT eCRF page.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) 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 (subject) 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 (CTCAE Grade 1-4)
2. Its duration (start and end dates)
3. Its relationship to the study treatment (reasonable possibility that AE is related: No, Yes)

4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1.

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

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.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors or as per Cheson's guidelines for hematological malignancies), should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

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 in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

8.1.3 Adverse events of special interest

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are ones of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them.

Adverse events of special interest are defined on the basis of an ongoing review of the safety data. AESIs are discussed in detail in the Investigator Brochure.

8.2 Serious adverse events

8.2.1 Definitions

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

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

8.2.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days for patients on the s.c formulation and 84 days for patients on the LAR formulation after the patient has stopped study treatment must be reported to IQVIA Safety office within 24 hours of learning of its occurrence. IQVIA, in its turn, will promptly inform Recordati.

Any SAE that begins or worsens after signing of the informed consent for the roll-over and during the safety follow up period defined in the parent protocol should be reported as an adverse event in both clinical databases; however, only one SAE report will be sent to IQVIA.

- Any SAE that begins or worsens **during** the safety follow-up period specified in the parent study should have an SAE report submitted to IQVIA with the parent protocol study number.
- Any SAE that begins or worsens **after** the safety follow-up period specified in the parent study should have an SAE report submitted to IQVIA with the roll-over protocol study number.

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes 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.

The date of the informed consent signed for this roll-over study (the roll-over date) is important to determine how SAEs should be reported:

- Any SAEs occurred prior to that date should be reported for the parent protocol, including all the follow up information relevant to such SAEs.
- New SAEs with an onset date after the roll-over date will be reported for this protocol.

It is important to use the right SAE form with the correct protocol number for these two scenarios, to avoid confusion in SAE processing. For a patient already on the roll-over protocol but follow up information is reported for the previous SAEs in the parent protocol, it must be clearly labeled that this is for the parent protocol number.

Any SAEs experienced after the 30 day/84 day safety evaluation follow-up period (or 5 half-lives, if half-life is established, whichever is longer) should only be reported to IQVIA if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. 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 submit the completed form within 24 hours to IQVIA. Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site.

Follow-up information is submitted in the same way as the original SAE Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Reference Safety Information section of the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Recordati study treatment, IQVIA (on behalf of Recordati) may urgently require further information from the investigator for Health Authority reporting. Recordati may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics

committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries. Recordati may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported.

8.3 Emergency unblinding of treatment assignment

Not applicable. This is an open-label study.

8.4 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to IQVIA within 24 hours of learning of its occurrence. IQVIA, in its turn, will promptly inform Recordati. 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 Trial Pregnancy Form and reported by the investigator to IQVIA. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

The protocol must specify how long the newborn will be followed up (just birth, or xyz months). Further advice on the length of post-natal follow up can be sought from Recordati and should be driven by the type of congenital abnormality expected.

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

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 pasireotide [Investigator Brochure]. For all other combination treatments, please refer to the relevant prescribing brochure for warnings and precautions. Additional safety information collected between [Investigator Brochure] updates will be communicated in the form of INs. 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

Not applicable.

8.7 Steering Committee

Not applicable.

9 Data collection and management

9.1 Data confidentiality

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

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

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

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

Prior to entering key sensitive personally identifiable information (Patient 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 Patient Initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the patient 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, Recordati personnel (or designated CRO, IQVIA) will review the protocol and eCRFs 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 eCRFs, 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 eCRFs 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 eCRF entries. IQVIA 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 eCRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

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

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

9.4 Database management and quality control

For studies using eCRFs, Recordati 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.

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

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

10 Statistical methods and data analysis

10.1 Analysis sets

The following analysis sets will be used for statistical analysis and data reporting.

10.1.1 Full Analysis Set

Not applicable.

10.1.2 Safety Set

The Safety Set includes all patients who received at least one dose of study medication after enrolling into the roll-over protocol.

10.1.3 Dose-determining analysis set

Not applicable.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data characteristics will be summarized descriptively for the Safety Set.

10.3 Treatments (study treatment, compliance)

Dose administration data will be summarized using the Safety Set.

10.4 Primary objective

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

10.4.1 Variable

See Section 10.5.3.

10.4.2 Statistical hypothesis, model, and method of analysis

No hypothesis will be tested.

10.4.3 Handling of missing values/censoring/discontinuations

Not applicable.

10.4.4 Supportive analyses

No supportive analysis will be performed.

10.5 Secondary objectives

10.5.1 Key secondary objective(s)

Not applicable.

10.5.2 Other secondary efficacy objectives

The secondary objective of the study is to evaluate clinical benefit as assessed by the investigator. Proportion of patients with clinical benefit as assessed by the investigator will be summarized at scheduled visits.

10.5.3 Safety objectives

The assessment of safety will be based mainly on the frequency and severity of AEs, AESI and SAEs.

10.5.3.1 Analysis set and grouping for the analyses

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

1. on-treatment period: from day of first dose of study medication in the roll-over study to 3 months (day 84) following the last dose of pasireotide LAR treatment and to 1 month (day 30) following the last dose of pasireotide s.c. treatment.
2. post-treatment period: starting at 3 months+1 day (day 85) following the last dose of pasireotide LAR treatment and at 1 month+1 day (day 31) following the last dose of pasireotide s.c. treatment.

10.5.3.2 Adverse events (AEs)

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

The incidence of treatment emergent adverse events will be summarized by system organ class and/or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment.

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

10.5.3.3 Other safety data

Not applicable.

10.5.3.4 Tolerability

Not applicable.

10.6 Interim analysis

This study has also been categorized as voluntary European Post Authorization Safety Study (PASS). Therefore, regular interim analyses will be performed during the course of the study as need by the Sponsor and will occur every 2 years beginning in 2017 and continuing until the study end. Details will be specified in the statistical analysis plan. The final analysis will occur when all patients complete the study.

10.7 Sample size calculation

Not applicable.

10.8 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. 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 IQVIA monitors, auditors, Recordati Clinical Quality Assurance representatives, designated agents of Recordati, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

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

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

IQVIA (on behalf of Recordati) will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Recordati before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the IQVIA monitor after IRB/IEC/REB approval.

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

Male participant will be asked to provide, the Female Partner of Male Participant form, to their partners.

Additional consent form

Not applicable.

11.4 Discontinuation of the study

Recordati–reserves the right to discontinue this study under the conditions specified in the clinical study agreement.

11.5 Publication of study protocol and results

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

11.6 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 patients. As part of participating in a Recordati-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, patients' 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 patient 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 case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

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

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

11.7 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 Recordati. 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 Recordati or designee or Health Authorities.

Recordati will delegate some trial-related activities to the CRO IQVIA. IQVIA has in place its own Quality Management System to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Recordati will maintain the oversight of any trial-related duties, functions and delegated activities that will be subcontracted to IQVIA.

11.9 Financial disclosures

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

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Recordati 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 Recordati 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 Recordati, 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, Recordati should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

13 References (available upon request)

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14 Appendices

14.1 Appendix 1: Medications known to be associated with QT interval prolongation

The list of drugs is generally recognized to have a possible association with QT prolongation can be found at //crediblemeds.org. This list is not considered to be all inclusive and any questions regarding the QT prolongation potential should be discussed with the Recordati Medical Monitor.

14.2 Appendix 2: Recommended hepatic safety management guidance

Patients with transaminase increase combined with TBIL increase may be indicative of potential DILI, and should be considered as clinically important events.

If any of the criteria below are observed at any routine examinations (standard of care),

- ALT or AST > 3 x ULN and Total Bilirubin ≥ 2 x ULN.
- ALT or AST > 5 x ULN and ≤ 8 x ULN.
- ALT or AST > 8 x ULN, patient should be discontinued.

The following should be performed immediately within **72 hours** of awareness of the abnormality (for further details refer to Figure 14-1):

- 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), Alb, 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.

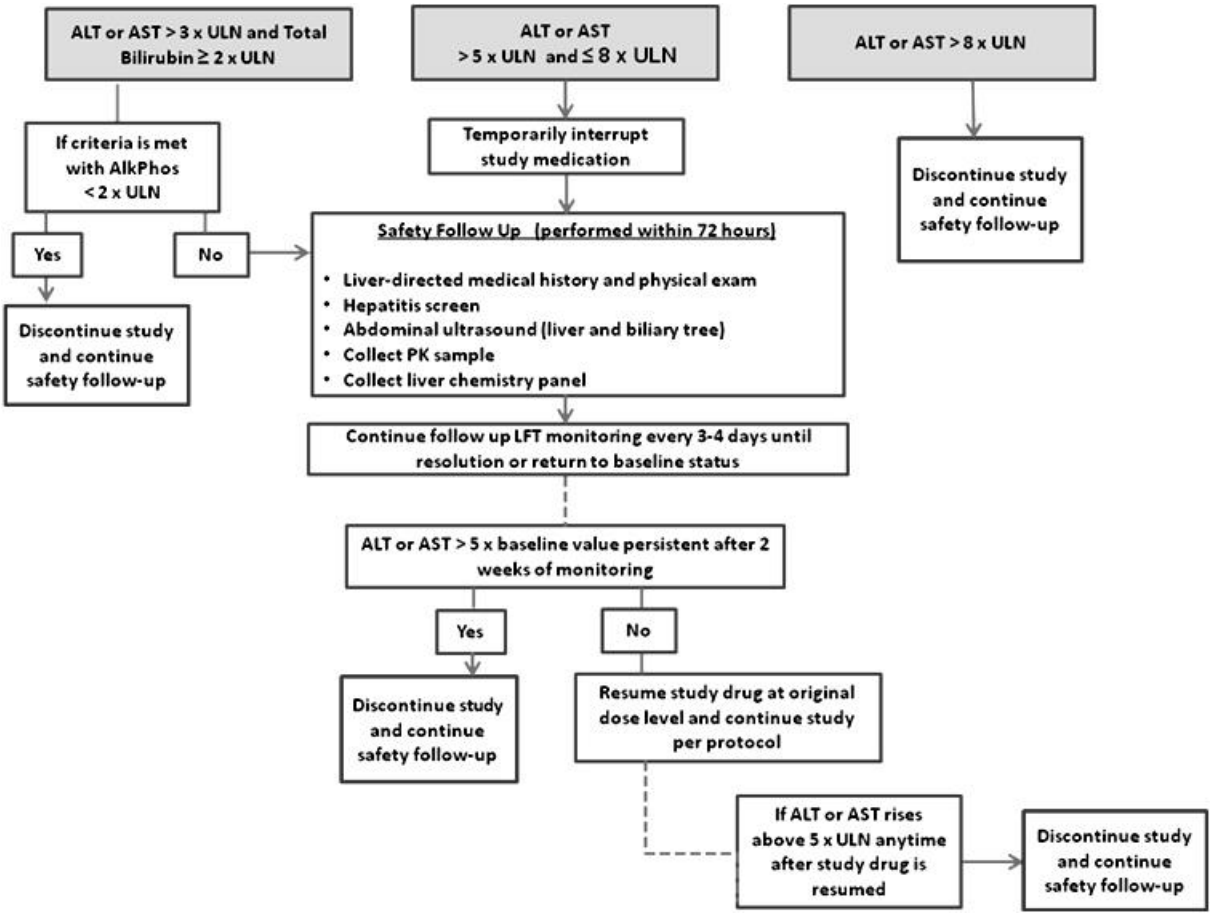
Patients or subjects may need to be discontinued if the abnormal liver function criteria are met upon LFT retesting. Progress reports of the event should be maintained until resolution or stabilization (i.e. no further elevation after 2 consecutive assessments).

For ALT or AST > 5 x ULN and ≤ 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 (ALT and AST ≤ 5 ULN) 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 any time 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 14-1 Recommended LFT management guidance



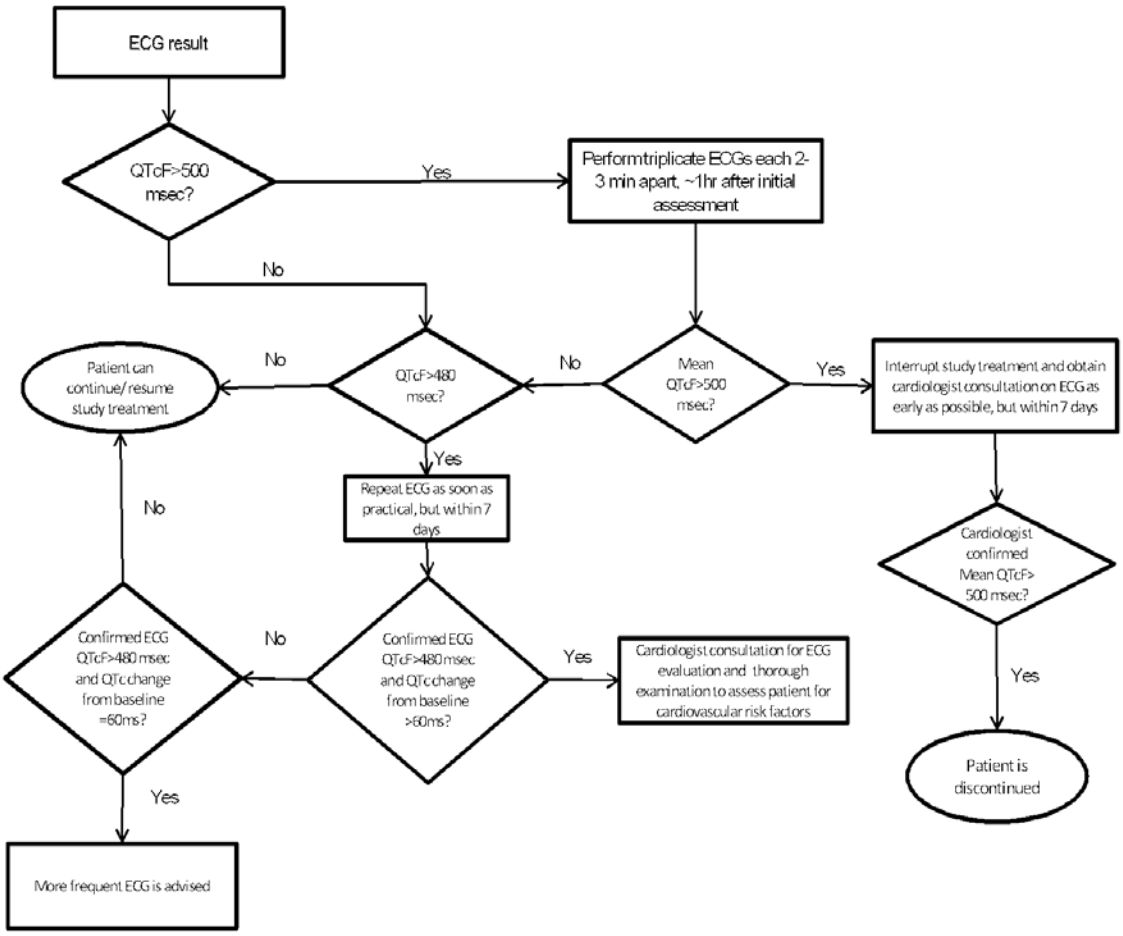
14.3 Appendix 3: Recommended guidance for follow up in case of QT-related findings during routine ECG

If at any routine ECG a QTcF> 500msec is observed, triplicate ECGs, each 2-3 minutes apart, need to be collected approximately 1 hour after the initial ECG. The mean QTcF from the triplicate ECGs will be determined and if the mean QTcF > 500msec, study treatment should be interrupted until a cardiologist has re-evaluated the ECG. Patient reassessment should be performed as early as possible but within 7 days of the initial abnormal ECG by a cardiologist for cardiovascular risk factors and a decision regarding study continuation.

If mean QTcF >480msec / ≤ 500msec is observed, the repeat ECG assessment must be performed as soon as practical but within 7 days of the initial abnormal ECG. In addition, the following steps need to be taken (for more details refer to Figure 14-2 below):

- If a QTcF >480msec / ≤ 500 msec is confirmed and QTcF change from pretreatment exceeds 60 msec, cardiology consultation must be sought as soon as practical (within 7 days) for ECG re-evaluation and clinical assessment for cardiovascular risk factors and a decision regarding study continuation.
- If a QTcF > 480msec / ≤ 500msec is confirmed and QTcF change from pretreatment < 60 ms, more frequent ECG follow-up is advised.

Figure 14-2 Recommended guidance for ECG follow up



14.4 Appendix 4: Recomended guidance for fasting blood glucose management

Hyperglycemia

Two clinical studies **([SOM230B2216] and [SOM230B2124])** have been conducted 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 indicate that pasireotide decreases insulin, GLP-1 and GIP secretion, particularly in the postprandial period. Results from SOM230B2124 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. In phase II and III studies, some patients with Cushing's disease, acromegaly or neuroendocrine tumor required insulin to treat hyperglycemia.

Glucose monitoring

All patients need to be educated on the signs and symptoms of hyperglycemia. Patients must monitor their fasting blood glucose by fingerstick at home. It is recommended that a diary of the blood glucose values is used for appropriate management throughout the study. The collected data should be presented to the physician/diabetes specialist for evaluation. This data will not be collected by the sponsor.

Blood glucose monitoring

Close and frequent glucose monitoring is recommended during pasireotide treatment.

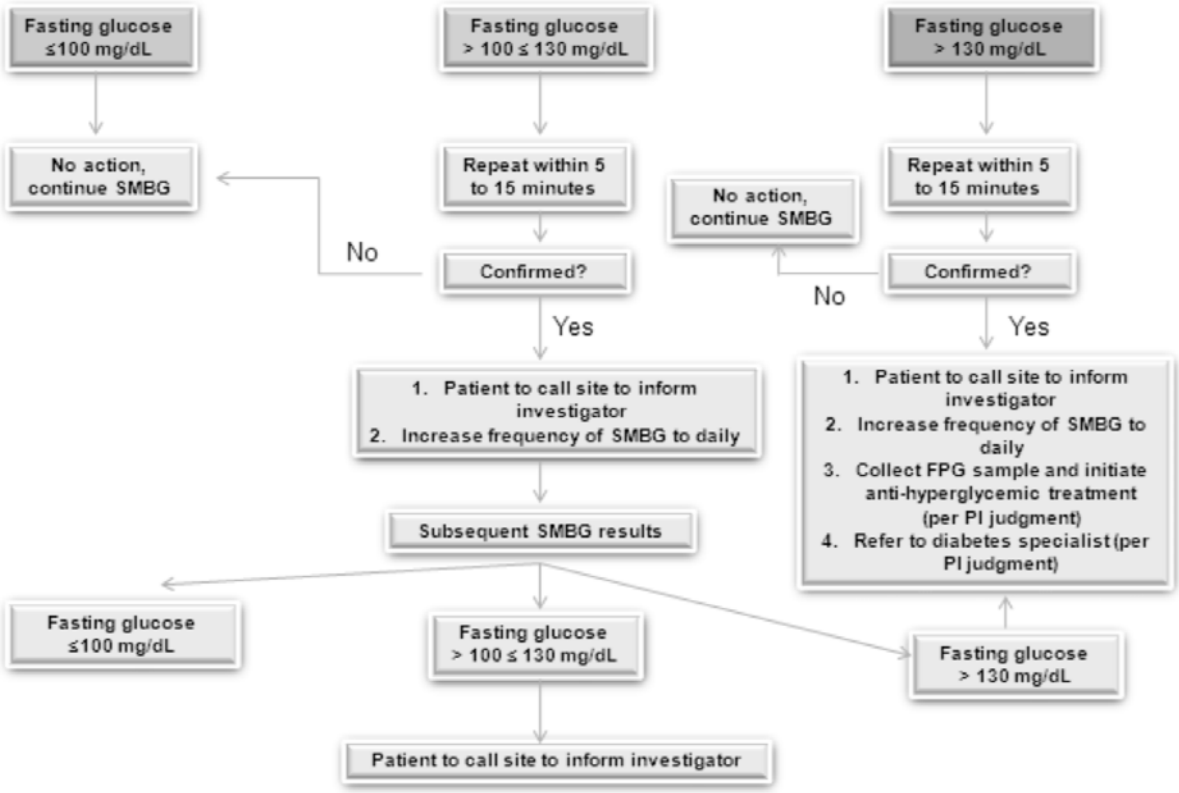
- If any fasting values above 100 mg/dL are observed, the guidelines in Figure 14-3 are to be followed. These guidelines are based on the current recommendations from the 2012 ADA and EASD aiming at a glycemic treatment goal of FPG <130 mg/dL (<7.2 mmol/L) (Inzucchi, SE et al. DiabetesCare June 2012 vol. 35 no. 6 1364-1379). 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 14-3.
- 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 can be collected prior to initiation of anti-hyperglycemic treatment.
- In case of dose increase, the glucose monitoring frequency should be increased following the recommendations described above at treatment initiation

FPG and HbA1c monitoring

- If FPG > 130 mg/dL or HbA1c ≥ 6.5 %, intervention for hyperglycemia needs to be implemented
- If FPG > 160 mg/dL or HbA1c >7.5%, despite optimal anti-diabetic therapy, referral to a diabetologist is recommended.
- If grade 3 hyperglycemia (FPG >250 mg/dL; >13.9 mmol/L) at any point in the study, despite appropriate anti-diabetic medication, pasireotide dose should be reduced
- If consistently high glucose values [FPG ≥ 240 mg/dL (13.3 mmol/L) or HbA1c ≥ 10 %] despite appropriate management of diabetes including diet and/or exercise with or without

optimal anti-diabetic therapy and study drug dose reduction, patient must be discontinued from study treatment as outlined in Section 7.1.5.1. After the last study dose was received, patients have to monitor their fasting blood glucose for 1 month

Figure 14-3 Recommended guidance for fasting self-monitoring blood glucose management



14.5 Appendix 5: Dose modification information for acromegaly or carcinoid patients receiving pasireotide LAR (from protocol CSOM230C2110, CSOM230C2305, CSOM230C2402 and CSOM230C2413)

At any time during the roll-over, the pasireotide LAR dose may be increased up to a maximum dose of 60 mg per injection if biochemical control is not achieved, i.e. when their GH level ≥ 2.5µg/L and/or IGF-1> ULN (age and sex related). Also the pasireotide LAR dose may be reduced if a patient is experiencing a drug related toxicity. The dose should be adjusted in 20 mg steps, e.g. the pasireotide LAR dose can be adjusted from 60 mg to 40 mg or from 40 mg to 20 mg. The decision to change the dose is to be made by the investigator or designee, and the dose change must be recorded in the Dosage Administration Record CRF. Patients should return to the previous dose once the tolerability issue resolves.

Study C2413 specific: The minimum dose to be administered is 10 mg for patients with IGF-1 levels falling below the lower limit of normal and have controlled mean GH levels. The IGF-1 values are required to be confirmed to be below LLN on two consecutive assessments. If biochemical control is maintained, the patient can continue on the lower dose for the remainder of the trial. If biochemical control is lost, the dose should be increased. The 10 mg dose should be obtained from the 20 mg vial.

Table 14-1 Dose modification for AEs, excluding LFT increase, QT prolongation and hyperglycemia

Adverse event	Action
CTCAE grade ≤ 2	No drug adjustments
CTCAE grade ≥ 3 and assessed as study drug related	Reduce pasireotide to the next lower dose level. • If the AE improves to grade ≤ 2 before the next administration, increase dose back to the prior dose. • If the dose is increased and the AE recurs at a grade ≥ 3, the dose should be reduced again. The patient should stay on this lower dose and no further dose titrations are allowed. • If the AE does not improve to grade ≤ 2, the dose is to be reduced further. If the AE does not improve to grade ≤ 2 on the minimum study dose, the treatment should be stopped.
For the management of LFT increase, QT prolongation, and hyperglycemia refer to specific instructions provided in Appendix 2, Appendix 3 and Appendix 4.	

Table 14-2 Dose adjustments for pasireotide LAR for patients from SOM230C2110

Dose (mg)	Volume to be injected
20 mg	2 x 10 mg vial + 2 mL vehicle: whole volume to be injected or 1 x 20 mg vial + 2 mL vehicle: whole volume to be injected
40 mg	1 x 40 mg vial + 2 mL vehicle: whole volume to be injected
60mg	2 x 10 mg vial + 1 x 40 mg vial + 2 mL vehicle; whole volume to be injected or 1 x 20 mg vial + 1 x 40 mg vial + 2 mL vehicle; whole volume to be injected

Table 14-3 Dose adjustments for pasireotide LAR for patients from SOM230C2305

Dose (mg)	Volume to be injected
20 mg	1 x 20mg vial + 2 mL vehicle, whole volume to be injected
40 mg	1 x 40mg vial + 2 mL vehicle, whole volume to be injected
60 mg	1 x 20mg + 1 x 40mg vial + 2 mL vehicle, whole volume to be injected

Table 14-4 Dose adjustments for pasireotide LAR for patients from SOM230C2402

Dose (mg)	Volume to be injected
40 mg	1 x 20 mg vial + 1 x 20 mg vial + 2 mL vehicle, whole volume to be injected
60 mg	1 x 20 mg + 1 x 40 mg vial + 2 mL vehicle, whole volume to be injected

14.6 Appendix 6: Dose modification information for Cushing's patients receiving pasireotide LAR (from protocol SOM230G2304)

Dose up-titration

Patients will receive the same dose of pasireotide LAR as the last dose in the parent study. The maximum dose to be administered is 40 mg. Dose can be increased from 10 to 30 mg and from 30 to 40 mg. During the roll-over study, the timing of the dose adjustments will be based on mUFC values, at the investigators discretion but must include a duration of at least 3 months on a current dose prior to up-titration and no tolerability issues are present. Patients receiving the 40 mg dose after Month 12 without tolerability issues that require a dose reduction will remain at this dose regardless of mUFC status (≤ 1x ULN or > 1 xULN).

Dose down-titration

Patients with tolerability issues can have their dose decreased as deemed necessary by the investigator (see Table 14-5). The dose can be increased again after the tolerability issue resolves. Patients unable to tolerate a minimum dose of 5 mg will be discontinued.

These changes must be recorded on the Dosage Administration Record CRF.

Table 14-5 Dose modification for AEs, excluding LFT increase, QT prolongation and hyperglycemia

Adverse event	Action
AE CTC grade ≤ 2	No drug adjustments
AE CTC grade ≥ 3 and assessed as study drug related	Reduce pasireotide LAR i.m. dose from: 40mg to 30 mg 30 mg to 10 mg 10 mg to 5mg 5mg - discontinue If AE improves to grade ≤ 2 before the next administration, increase dose to that prior to the dose reduction unless investigator opinion is to remain on current dose. If the dose is increased and the AE recurs at CTC grade ≥ 3, the dose should be reduced again and the patient should stay on this lower dose and no further dose titrations are allowed. During the first 7 months of treatment, only 1 blinded dose decrease is allowed. If the AE persists at grade ≥ 3 after reduction, the patient is to be discontinued. After the first 7 months, If AE does not improve to grade ≤ 2 the dose is to be reduced further until the 5 mg dose is reached. If the AE does not improve to grade ≤ 2 on the minimum dose (5 mg) the patient will be withdrawn.
For the management of LFT increase, QT prolongation, and hyperglycemia refer to specific instructions provided in Appendix 2, Appendix 3 and Appendix 4.	

14.7 Appendix 7: Dose modification information for dumping syndrome patients receiving pasireotide s.c or LAR (from protocol SOM230X2203)

During the roll-over, dose increase will be allowed up to 60 mg (30, 40 and 60 mg) in the event that control is lost (glucose levels < 60 mg/dL at 90,120, 150 **or** 180 min during the OGTT or presence of symptoms). The up- titration must be in increments of 10 mg with the exception of patients receiving 40 mg when an increment of 20 mg (from 40 mg to 60 mg) is allowed.

In case a dose reduction is needed due to toxicity (Table 14-8), the dose can be reduced to the immediate lower dose level (Table 14-7) **and can be kept at this level if necessary. The lowest dose level allowed is 10 mg**. In case a dose reduction is needed due to toxicity at 10mg, the patient can have a dose interruption up to 28 days from the intended day of the scheduled dose or can be discontinued and followed up for toxicity as defined in Table 14-6. If a patient requires a dose interruption of more than 28 days due to toxicity, then the patient must be discontinued from the study and followed up for toxicity Table 14-6. When treatment is interrupted or permanently discontinued due to an AE or abnormal laboratory value the patient must be followed at least once a week for 4 weeks, and subsequently in 4-week intervals, until resolution or stabilization of the event, whichever occurs first.

Patients will be followed for adverse events and serious adverse events for 56 days following the last dose of pasireotide LAR treatment and for 28 days in case of discontinuation during pasireotide s.c. treatment.

Table 14-6 outlines the follow-up required for toxicities of specific types and CTCAE grades-

Table 14-6 Follow up evaluation (after treatment interruption)

Toxicity	Follow-up evaluation (after treatment interruption)
Hematology	If ≥ CTCAE grade 3 neutropenia or ≥ CTCAE grade 3 thrombocytopenia has been demonstrated, these parameters must be assessed at least twice a week until resolution to ≤ CTCAE grade 1 and then at least weekly until stabilization.
Renal	If serum creatinine ≥ 2 x ULN has been demonstrated, this parameter must be assessed at least twice a week until resolution to ≤ CTCAE grade 1 or baseline to and then at least weekly until stabilization.
Hepatic	For details on hepatic safety management, please refer to Appendix 2: Hepatic Safety Management
Pancreatic	If amylase and/or lipase ≥ CTCAE grade 3 has been demonstrated, these parameters must be assessed once at 2-4 days and once again at 7 days (± 1 day) and be repeated twice a week until resolution to ≤ CTCAE grade 2 and then at least weekly until stabilization. A CT scan or other imaging study to assess the pancreas, liver and gallbladder must be performed within 1 week of the first occurrence of any ≥ CTCAE grade 3 of amylase and/or lipase. In patients with serum triglycerides ≥ 500 mg/dL, urine amylase needs to be tested.
Endocrine/ metabolic	For details on hyperglycemia management, please refer to Appendix 4: 'Fasting blood glucose management'.
Cardiac	For details on the follow-up and treatment of QT prolongation, please refer to Appendix 3 'Recommended follow up in case of QT-related findings during routine ECG'
Non-laboratory	Patients who experience non-laboratory AEs must be evaluated at least once a week following demonstration of the toxicity until resolution of the toxicity until stabilization of the toxicity, or until study completion.

Table 14-7 Dose reduction steps for pasireotide LAR monthly dosing q28d

Dose reduction*			
	Dose level - 0	**Dose level - 1**	**Study Phase**
Pasireotide LAR	60 mg q28d	40 mg q28d	Extension phase
Pasireotide LAR	40 mg q28d	30 mg q28d	Extension phase
Pasireotide LAR	30 mg q28d	20 mg q28d	Extension phase
Pasireotide LAR	20 mg q28d	10 mg q28d ***	LAR or Extension phases

*Dose reduction should be based on the worst toxicity demonstrated at the last dose.
*** The lowest dose allowed 10 mg.

Table 14-8 Dose modification for AEs, excluding LFT increase, QT prolongation and hyperglycemia

Adverse event	Action
CTCAE grade ≤ 2	No drug adjustments
CTCAE grade ≥ 3 and assessed as study drug related	Reduce pasireotide to the next lower dose level. • If the AE improves to grade ≤ 2 before the next administration, increase dose back to the prior dose. • If the dose is increased and the AE recurs at a grade ≥ 3, the dose should be reduced again. The patient should stay on this lower dose and no further dose titrations are allowed. • If the AE does not improve to grade ≤ 2, the dose is to be reduced further. If the AE does not improve to grade ≤ 2 on the minimum study dose, the treatment should be stopped.
For the management of LFT increase, QT prolongation, and hyperglycemia refer to specific instructions provided in Appendix 2, Appendix 3 and Appendix 4.	

14.8 Appendix 8: Dose modification information for patients with metastatic melanoma or metastatic Merkel cell carcinoma receiving pasireotide s.c (from protocol SOM230X2404)

Patients will continue receiving the dose of pasiroetide LAR q28 d at the same dose received during the follow-up period (20, 40, 60 or 80 mg).

In case a dose reduction is needed due to toxicity, the dose can be reduced to the immediate lower dose level (from 80 mg q 28 d to 60 mg q 28 d, from 60 mg q 28 d to 40 mg q 28 d, and from 40 mg q 28 d to 20 mg q 28 d) and can be kept at this level if necessary for the duration of the study or until disease progression or death. However, the dose will not be re-escalated once reduced. In case patients receiving 20 mg q 28 d need to reduce the dose further, they should be discontinued from the study. If a patient requires a dose interruption of > 7 consecutive days from the intended day of the scheduled dose, then the patient must be discontinued from the study and only follow up for toxicity defined in (reference **table below**).

When treatment is interrupted or permanently discontinued due to an AE or abnormal laboratory value the patient must be followed at least once a week for 4 weeks, and subsequently in 4-week intervals, until resolution or stabilization of the event, whichever occurs first.

Patients who experience non-laboratory AEs should be evaluated at least once a week following demonstration of the toxicity until a resolution of the toxicity or study treatment completion occurs.

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. (reference **table below**) 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 (reference **table below**).

Table 14-9 Dose modification for AEs, excluding LFT increase, QT prolongation and hyperglycemia for patients from protocol SOM230X2402

Patients	Adverse event	Action
All	AE grade ≤ 2 (mild to moderate)	No drug adjustments
	AE grade ≥ 3 (severe to life-threatening) and judged as drug related*#	Reduce dose by 20 mg q 28 d to the next dose level as described above in this appendix (Appendix 8). Once the dose is reduced, the patient will stay on the lowered dose for the entire duration of the roll-over If AE recurs at grade ≥ 3, reduce dose by 20 mg q 28 d again and remain at lower dose. If AE does not improve to grade ≤ 2 the dose is to be reduced further (following the guidance as described above in this appendix (Appendix 8). If the AE does not improve to grade ≤ 2 on the minimum dose (20 mg q 28 d), patient is to discontinue treatment and followed for safety.
For the management of LFT increase, QT prolongation, and hyperglycemia refer to specific instructions provided in Appendix 2, Appendix 3 and Appendix 4. For management of diarrhea, please refer to (reference below section)		

14.8.1 Guidance for diarrhea management

General recommendations:

- Stop all lactose-containing products, alcohol
- Stop laxatives, bulk fiber (Metamucil, Procter & Gamble), and stool softeners (docusate sodium; Colace, Roberts)
- Drink 8 to 10 large glasses of clear liquids per day (water, Pedialyte (Ross),Gatorade (Quaker), broth)
- Eat frequent small meals (bananas, rice, applesauce, Ensure, toast)
- Stop high-osmolar food supplements such as Ensure Plus and Jevity Plus (with fiber)

It is recommended that patients be provided loperamide tablets. It is mandatory that patients are instructed on the use of loperamide at cycle 1 in order to manage signs or symptoms of diarrhea at home. Patients should be instructed to start oral loperamide (initial administration of 4mg, then 2mg every 4 hours (maximum of 16 mg/day) at the first sign of loose stool or symptoms of abdominal pain. These instructions should be provided at each cycle and the site should ensure that the patient understood the instruction. At the beginning of each cycle, each patient should be specifically questioned regarding any experience of diarrhea or diarrhea related symptoms. If symptoms were experienced, then the site should question the patient regarding the actions taken for these symptoms.

Treatment of diarrhea grade 1 or 2

Diarrhea grade 1 or 2 will be treated with standard loperamide (initial at first administration 4 mg, then 2 mg every 4 hours (maximum of 16 mg/day) or after each unformed stool).

12-24 hours later:

Diarrhea resolved

- Continue instructions for dietary modification
- Gradually add solid foods to diet
- Discontinue loperamide after 12-hours diarrhea-free interval

Diarrhea unresolved

Persisting diarrhea grade 1 or 2 will be treated with addition of opium tincture or dihydrocodeine tartrate tablets/injections with monitoring of patients condition to rule out dehydration, sepsis, ileus) medical check and selected workup if patient does not need hospitalization (see section Diarrhea workup and additional test in the particular trial protocol). Observe patient for response to antidiarrheal treatment.

Persisting diarrhea grade 3 or 4 may be treated with hospitalization, high dose loperamide (initial 4 mg, then 2 mg every 2 hours) and addition of opium tincture or dihydrocodeine tartrate tablets/injections, start of *i.v.* fluids and antibiotics as needed with monitoring of patients condition (to rule out dehydration, sepsis, ileus) medical check and workup (perform appropriate additional testing). Observe patient for response.

After 12-24 hours:

Diarrhea resolved

- Continue instructions for dietary modification
- Gradually add solid foods to diet
- Discontinue loperamide and/or other treatment after 12-hours diarrhea-free interval

Diarrhea unresolved

- If diarrhea still persisting (NCI CTC grades 1 and 2), after 2x 24 hours with high dose loperamide and opiates then admit to hospital and employ measures as for grade 3 and 4 until diarrhea resolved
- If diarrhea still persisting and progressed to NCI grades 3 and 4, employ measures described below.

Treatment of diarrhea grade 3 or 4

Severe diarrhea grade 3 or 4 may be treated with hospitalization, high dose loperamide (initial 4 mg, then 2 mg every 2 hours and addition of opium tincture or dihydrocodeine tartrate tablets/injections, start of *i.v.* fluids and antibiotics as needed with monitoring of patients condition (to rule out dehydration, sepsis, ileus) medical check and workup (see section Diarrhea workup and additional test in the particular trial protocol). Observe patient for response.

After 12-24 hours:

- If diarrhea persisting administer s.c. Sandostatin/octreotide (100-500 μg tid)

- Continue IV fluids and antibiotics as needed
- If diarrhea grade 3 or 4 still persists patients should receive opium tincture or dihydrocodeine tartrate injections s.c. or i.m.
- If diarrhea grade 3 or 4 is still persisting s.c. Sandostatin/octreotide (500-1000 µg tid) should be administered.
- To control and/or resolve diarrhea, next cycle of treatment should be delayed by 1 or 2 weeks. Treatment should be continued only when diarrhea resolved.

Diarrhea workup

Perform appropriate tests (Fine and Schiller 1999).

Spot stool analysis

- Collect stool separating it from urine (special containers, analysis immediately, exceptionally freeze samples)
- Blood
- Fecal leukocytes (Wright's staining and microscopy) or
- Clostridium difficile toxin
- Fecal cultures including Salmonella spp., Campylobacter spp., Giardia, Entamoeba, Cryptosporidium (which can lead to opportunistic infections in immonunosuppressed patients), plus Shigella and pathogenic E. coli - enterotoxigenic, enterohemorrhagic etc., possibly Aeromonas, Pleisiomonas (if suspected exposure to contaminated water)

Endoscopic examinations

Endoscopic examinations may be considered **only if absolutely necessary**. The bowel is likely to be fragile with evidence of colitis and thus great care and caution must be exercised in undertaking these invasive procedures.

- Gastroscopy to obtain jejunal fluid - re. bacterial overgrowth for cultures and biopsy of proximal jejunum to assess extent of inflammatory jejunitis
- Sigmoidoscopy - reassessment of colitis

14.8.2 Dose and treatment schedule

Study treatments in the follow-up phase	Pharmaceutical form and route of administration	Total Monthly Dose	Frequency and/or Regimen	Vials Used
Pasireotide LAR, im	intramuscular (i.m.)	20mg	20 mg q 28 d	1 vial of 20 mg powder, (+1 vial of 2 ml vehicle)
Pasireotide LAR, im	intramuscular (i.m.)	40 mg	40 mg q 28 d	1 vial of 40 mg powder, (+1 vial of 2 ml vehicle)
Pasireotide LAR, im	intramuscular (i.m.)	60 mg	60 mg q 28 d	1 vial of 20 mg + 1 vial of 40 mg or 1 vial of 60 mg powder, (+ 1 vial of 2 ml vehicle)
Pasireotide LAR, im	intramuscular (i.m.)	80 mg	80 mg q 28 d	2 vials of 40 mg powder, (+ 1 vial of 2 ml vehicle)

14.9 Appendix 9: Dose modification information for patients with rare tumors of neuroendocrine origin receiving pasireotide LAR (from protocol SOM230D2203)

For patients who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to keep the patient on study drug.

Study drug for this study will be pasireotide LAR at 60 mg every 28 days. If tolerability issues occur, the treatment dose may be reduced to pasireotide LAR at 40 mg with next scheduled injection. A patient receiving 40 mg showing further tolerability issues may reduce the dose level to 20 mg at the next injection. The investigator may, at his or her discretion, increase the patient's dose of study medication after resolution of tolerability issue. However, patients not able to tolerate the minimum pasireotide LAR dose of 20 mg will be discontinued from study.

Patients who have not achieved symptom control or in whom adequate control is not maintained are permitted to use rescue dose of pasireotide s.c. up to 600 µg b.i.d to control their symptoms at anytime during the study duration. If tolerability issues arise upon use of s.c. injections for rescue purposes, these injections should be stopped. Once the tolerability issue has resolved, the s.c. injections may be resumed if needed. The rescue s.c. dose may not exceed 600 µg b.i.d.

All dose changes must be recorded on the Dosage Administration Record CRF.

Table 14-10 Dose modification for AEs, excluding LFT increase, QT prolongation and hyperglycemia

Adverse event	Action
CTCAE grade ≤ 2	No drug adjustments
CTCAE grade ≥ 3 and assessed as study drug related	Reduce pasireotide to the next lower dose level. • If the AE improves to grade ≤ 2 before the next administration, increase dose back to the prior dose. • If the dose is increased and the AE recurs at a grade ≥ 3, the dose should be reduced again. The patient should stay on this lower dose and no further dose titrations are allowed. • If the AE does not improve to grade ≤ 2, the dose is to be reduced further. If the AE does not improve to grade ≤ 2 on the minimum study dose, the treatment should be stopped.
For the management of LFT increase, QT prolongation, and hyperglycemia refer to specific instructions provided in Appendix 2, Appendix 3 and Appendix 4.	

14.10 Appendix 10: Dose modification information for patients with neuroendocrine tumors receiving pasireotide LAR (from protocol SOM230D2101)

Patients continuing into the roll-over study will receive the same dose of pasireotide LAR every 28 days as the last dose administered during the parent study.

When treatment is interrupted or permanently discontinued due to an AE or abnormal laboratory value the patient must be followed at least once a week for 8 weeks, and subsequently in 4-week intervals, until resolution or stabilization of the event, whichever comes first. If a patient requires a dose delay of > 21 days from the intended day of the scheduled dose, then the patient must be discontinued from the study. However, the patient will be followed up for toxicity as previously described. All patients will be followed for adverse events and serious adverse events for at least 56 days following the last dose of pasireotide LAR treatment.

Table 14-11 outlines the follow-up required for toxicities of specific types and CTCAE grades.

Table 14-11 Follow-up evaluations for selected toxicities

Toxicity	Follow-up evaluation
Hematology	If ≥ CTCAE grade 3 neutropenia or ≥ CTCAE grade 3 thrombocytopenia have been demonstrated, these parameters must be repeated at least twice a week until resolution to ≤ CTCAE grade 1 to allow for initiation of re-treatment, and then at least weekly until either initiation of retreatment or until stabilization.
Renal	If serum creatinine ≥ 2 x ULN has been demonstrated, this parameter must be repeated at least twice a week until resolution to ≤ CTCAE grade 1 or baseline to allow for initiation of re-treatment, and then at least weekly until either initiation of re-treatment or until stabilization.
Hepatic	For details on hepatic safety management, please refer to Appendix 2: Hepatic Safety Management
Pancreatic	If amylase and/or lipase ≥ CTCAE grade 3 has been demonstrated, these parameters must be assessed once at 2-4 days and once again at 7 days (± 1 day) and be repeated twice a week until resolution to ≤ CTCAE grade 2 to allow for initiation of re-treatment, and then at least weekly until either resolution to ≤ CTCAE grade 1 or until stabilization. A CT scan or other imaging study to assess the pancreas, liver and gallbladder must be performed within 1 week of the first occurrence of any ≥ CTCAE grade 3 of amylase and/or lipase. In patients with serum triglycerides ≥ 500 mg/dL, urine amylase needs to be tested.
Endocrine/ metabolic	For details on hyperglycemia management, please refer to Appendix 4: 'Fasting blood glucose management'.
Cardiac	For details on the follow-up and treatment of QT prolongation, please refer to Appendix 3 'Recommended follow up in case of QT-related findings during routine ECG'
Non-laboratory	Patients who experience non-laboratory DLTs must be evaluated at least once a week following demonstration of the toxicity until resolution of the toxicity to allow for re-treatment, until stabilization of the toxicity, or until study completion.

14.10.1 Dose modification and dose delay

The patient should be followed as described in Table 14-12 until the toxicity in question has resolved to CTCAE grade 1 or to the patients' baseline value, or until the toxicity is deemed irreversible.

Patients who cannot be treated with pasireotide LAR within 21 days of the intended dosing day due to drug-related toxicity should have weekly follow-ups that include a physical examination, vital signs including weight, performance status, ECGs, and assessment of adverse events and concomitant medication. Following toxicity, ECG, hematology, renal and liver function tests should be performed as appropriate.

If a patient requires a dose delay of > 21 days from the intended day of the next scheduled dose of pasireotide LAR, then the patient must be discontinued from the study. Patients who discontinue from the study for a study drug-related adverse event or an abnormal laboratory value, must be followed as described in Table 14-11.

For each patient, only one dose reduction will be allowed after which the patient should be discontinued from the study. For each patient, once a dose level reduction has occurred, the dose level may not be re-escalated during subsequent treatment cycles with pasireotide LAR. Dose reduction for pasireotide LAR means treatment at a lower pasireotide LAR dose level. Dose modification for patients treated at the starting dose of 80 mg will be 60 mg.

All interruptions or changes to study drug administration must be recorded on the Dosage and Administration Record eCRF.

14.10.2 Treatment interruption and treatment discontinuation

All dose modifications should be based on the worst preceding toxicity.

Each patient is only allowed one dose reduction. In addition, a patient must discontinue treatment with pasireotide LAR if, after treatment is resumed at a lower dose, the toxicity recurs with the same or worse severity

Table 14-12 Criteria for interruption and re-initiation of pasireotide LAR

Recommended dose modifications for pasireotide LAR	
Worst toxicity CTCAE Grade* (value)	**Recommended dose modification any time during a cycle of therapy**
No toxicity	Maintain dose level
Hematologic	
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1500/mm^3)	Maintain dose level
Grade 2 (ANC < 1500 - 1000/mm^3)	Maintain dose level
Grade 3 (ANC < 1000 - 500/mm^3)	Omit dose until resolved to ≤ Grade 2, then - If resolved ≤ 7 days, then maintain dose level - If resolved > 7 days, then ↓ 1 dose level

Recommended dose modifications for pasireotide LAR	
Worst toxicity CTCAE Grade* (value)	**Recommended dose modification any time during a cycle of therapy**
Grade 4 (ANC < 500/mm^3)	Omit dose until resolved to ≤ Grade 2, then - If resolved ≤ 7 days, then maintain dose level - If resolved > 7 days, then ↓ 1 dose level
Thrombocytopenia	
Grade 1 (PLT < LLN - 75,000/mm^3)	Maintain dose level
Grade 2 (PLT < 75,000 - 50,000/mm^3)	Maintain dose level
Grade 3 (PLT < 50,000 - 25,000/mm^3)	Omit dose until resolved to ≤ Grade 1, then - If resolved ≤ 7 days, then maintain dose level - If resolved > 7 days, then ↓ 1 dose level
Grade 4 (PLT < 25,000/mm^3)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.5°C)	Omit dose until resolved, then ↓ 1 dose level
Renal	
Serum creatinine	
< 2 x ULN	Maintain dose level
2-3 x ULN	Omit dose until resolved to ≤ Grade 1, then - If resolved ≤ 7 days, then maintain dose level - If resolved > 7 days, then ↓ 1 dose level
Grade 3 (> 3.0 - 6.0 x ULN)	Omit dose and discontinue patient from study treatment
Grade 4 (> 6.0 x ULN)	Omit dose and discontinue patient from study treatment
Hepatic	
Bilirubin	
< 2 x ULN	Maintain dose level
2-3 x ULN	Omit dose until resolved to ≤ Grade 1, then - If resolved ≤ 7 days, then maintain dose level - If resolved > 7 days, then ↓ 1 dose level
Grade 3 (> 3.0 - 10.0 x ULN)	Omit dose until resolved to ≤ Grade 1, then - If resolved ≤ 7 days, then maintain dose level - If resolved > 7 days, then ↓ 1 dose level
Grade 4 (> 10.0 x ULN)	Omit dose and discontinue patient from study treatment **NOTE**: If grade 3 or 4 hyperbilirubinemia is due to the indirect (unconjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g. review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level and continue treatment at the discretion of the investigator
AST or ALT	
Grade 1 (> ULN - 2.5 x ULN)	Maintain dose level
Grade 2 (> 2.5 - 5.0 x ULN)	Maintain dose level

Recommended dose modifications for pasireotide LAR	
Worst toxicity CTCAE Grade* (value)	**Recommended dose modification any time during a cycle of therapy**
(>5.0 and ≤ 8 x ULN)	If ALT or AST return to less than 5 x ULN study drug can be resumed and patient can continue study per protocol. If persistent for more than 14 days, discontinue patient from study treatment. In the event of a re-occurrence, discontinue patient from study treatment.
(> 8 x ULN)	Omit dose and discontinue patient from study treatment
Pancreatic	
Pancreatitis Grade 1 Grade 2 Grade 3 Grade 4	 Maintain dose level Maintain dose level Omit dose and discontinue patient from study treatment Omit dose and discontinue patient from study treatment
Amylase and/or lipase Grade 1 (> ULN - 1.5 x ULN) Grade 2 (> 1.5 - 2.0 x ULN) Grade 3 (> 2.0 - 5.0 x ULN) Grade 4 (> 5.0 x ULN)	 Maintain dose level Maintain dose level **For asymptomatic**: Omit dose until resolved to ≤ Grade 1, then - If resolved ≤ 7 days, then maintain dose level - If resolved > 7 days, then ↓ 1 dose level **For symptomatic**: Omit dose and discontinue patient from study treatment Omit dose and discontinue patient from study treatment A CT scan or other imaging study to assess the pancreas, liver and gallbladder must be performed within 1 week of the first occurrence of any ≥ CTCAE grade 3 of amylase and/or lipase.
Endocrine/metabolic	
Fasting plasma glucose (FPS) or 2-hour postprandial capillary glucose (PPG) FPG <126 mg/dL or PPG < 140 mg/dL Grade 1 (> ULN – 160 mg/dL) Grade 2 (> 160 – 250 mg/dL) Grade 3 (> 250 – 500 mg/dL) Grade 5 (> 500 mg/dL)	 Maintain dose level Please refer to Appendix 14.2 ‘Guideline for study drug-induced hyperglycemia’
Cardiac	
Cardiac - prolonged QTc interval - QTcF > 480 ms and ≤ 500 ms	 If at any time a QTcF > 480 ms and ≤ 500 ms is observed a cardiology consultation must be sought to re-evaluate the abnormal ECG finding.

Recommended dose modifications for pasireotide LAR	
Worst toxicity CTCAE Grade* (value)	**Recommended dose modification any time during a cycle of therapy**
- QTcF > 500 msec	1. Triplicate ECGs (2-3 minutes apart) need to be taken approximately 1 hour after the initial ECG. 2. If the mean QTcF is > 500 ms, the patient must postpone study treatment until a cardiologist has re-evaluated the ECG. 3. The re-evaluation of ECG needs to be done as soon as practical but within 7 days of the initial abnormal ECG. 4. If the cardiologist confirms a mean QTcF > 500 ms, the patient must be discontinued.
Cardiac general	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4	Omit dose and discontinue patient from study treatment
Other adverse events	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4	Omit dose and discontinue patient from study treatment

14.10.3 Guidance for diarrhea management

General recommendations:

- Stop all lactose-containing products, alcohol
- Stop laxatives, bulk fiber (Metamucil, Procter & Gamble), and stool softeners (docusate sodium; Colace, Roberts)
- Drink 8 to 10 large glasses of clear liquids per day (water, Pedialyte (Ross),Gatorade (Quaker), broth)
- Eat frequent small meals (bananas, rice, applesauce, Ensure, toast)
- Stop high-osmolar food supplements such as Ensure Plus and Jevity Plus (with fiber)

It is recommended that patients be provided loperamide tablets. It is mandatory that patients are instructed on the use of loperamide at cycle 1 in order to manage signs or symptoms of diarrhea at home. Patients should be instructed to start oral loperamide (initial administration of 4mg, then 2mg every 4 hours (maximum of 16 mg/day) at the first sign of loose stool or symptoms of abdominal pain. These instructions should be provided at each cycle and the site should ensure that the patient understood the instruction. At the beginning of each cycle, each patient should be specifically questioned regarding any experience of diarrhea or diarrhea related symptoms. If symptoms were experienced, then the site should question the patient regarding the actions taken for these symptoms.

Treatment of diarrhea grade 1 or 2

Diarrhea grade 1 or 2 will be treated with standard loperamide (initial at first administration 4 mg, then 2 mg every 4 hours (maximum of 16 mg/day) or after each unformed stool).

12-24 hours later:

Diarrhea resolved

- Continue instructions for dietary modification
- Gradually add solid foods to diet
- Discontinue loperamide after 12-hours diarrhea-free interval

Diarrhea unresolved

Persisting diarrhea grade 1 or 2 will be treated with addition of opium tincture or dihydrocodeine tartrate tablets/injections with monitoring of patients condition to rule out dehydration, sepsis, ileus) medical check and selected workup if patient does not need hospitalization (see section Diarrhea workup and additional test in the particular trial protocol). Observe patient for response to antidiarrheal treatment.

Persisting diarrhea grade 3 or 4 may be treated with hospitalization, high dose loperamide (initial 4 mg, then 2 mg every 2 hours) and addition of opium tincture or dihydrocodeine tartrate tablets/injections, start of *i.v.* fluids and antibiotics as needed with monitoring of patients condition (to rule out dehydration, sepsis, ileus) medical check and workup (perform appropriate additional testing). Observe patient for response.

After 12-24 hours:

Diarrhea resolved

- Continue instructions for dietary modification
- Gradually add solid foods to diet
- Discontinue loperamide and/or other treatment after 12-hours diarrhea-free interval

Diarrhea unresolved

- If diarrhea still persisting (NCI CTC grades 1 and 2), after 2x 24 hours with high dose loperamide and opiates then admit to hospital and employ measures as for grade 3 and 4 until diarrhea resolved
- If diarrhea still persisting and progressed to NCI grades 3 and 4, employ measures described below.

Treatment of diarrhea grade 3 or 4

Severe diarrhea grade 3 or 4 may be treated with hospitalization, high dose loperamide (initial 4 mg, then 2 mg every 2 hours and addition of opium tincture or dihydrocodeine tartrate tablets/injections, start of *i.v.* fluids and antibiotics as needed with monitoring of patients condition (to rule out dehydration, sepsis, ileus) medical check and workup (see section Diarrhea workup and additional test in the particular trial protocol). Observe patient for response.

After 12-24 hours:

- If diarrhea persisting administer s.c. Sandostatin/octreotide (100-500 μg tid)

- Continue IV fluids and antibiotics as needed
- If diarrhea grade 3 or 4 still persists patients should receive opium tincture or dihydrocodeine tartrate injections s.c. or i.m.
- If diarrhea grade 3 or 4 is still persisting s.c. Sandostatin/octreotide (500-1000 µg tid) should be administered.
- To control and/or resolve diarrhea, next cycle of treatment should be delayed by 1 or 2 weeks. Treatment should be continued only when diarrhea resolved.

Diarrhea workup

Perform appropriate tests (Fine and Schiller 1999).

Spot stool analysis

- Collect stool separating it from urine (special containers, analysis immediately, exceptionally freeze samples)
- Blood
- Fecal leukocytes (Wright's staining and microscopy) or
- Clostridium difficile toxin
- Fecal cultures including Salmonella spp., Campylobacter spp., Giardia, Entamoeba, Cryptosporidium (which can lead to opportunistic infections in immonunosuppressed patients), plus Shigella and pathogenic E. coli - enterotoxigenic, enterohemorrhagic etc., possibly Aeromonas, Pleisiomonas (if suspected exposure to contaminated water)

Endoscopic examinations

Endoscopic examinations may be considered **only if absolutely necessary**. The bowel is likely to be fragile with evidence of colitis and thus great care and caution must be exercised in undertaking these invasive procedures.

- Gastroscopy to obtain jejunal fluid - re. bacterial overgrowth for cultures and biopsy of proximal jejunum to assess extent of inflammatory jejunitis
- Sigmoidoscopy - reassessment of colitis

14.11 Appendix 11: Dose modification information for patients with Cushing's receiving pasireotide s.c or acromegaly receiving pasireotide LAR (from protocols SOM230B2219 and SOM230B2305)

Cushing's disease: Pasireotide (SOM230) s.c. injection: 300, 600 or 900 µg b.i.d.; Acromegaly: Pasireotide (SOM230) i.m. LAR: 20, 40 or 60 mg every 28 days

14.11.1 Dose modifications for patients from protocol SOM230B2219

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. The following guidelines need to be applied:

Cushing's disease: At any time during the study the pasireotide dose may be reduced by 300 µg b.i.d for safety or tolerability reasons. Dose may be increased to 600 or 900 µg b.i.d if tolerability issues have resolved per investigator's discretion.

Acromegaly: Dose up-titration of pasireotide LAR to 60 mg i.m. once/28 days will be allowed in patients without adequate levels of GH and IGF-1 (no reduction of mean GH level to <2.5 µg/L and no normalization of IGF-1 to within normal limits (age and sex related)) as determined locally. A dose reduction by 20 mg will be permitted in case of tolerability issues, but the patient may return to previous dose once tolerability issues are resolved.

Dose should also be modified for adverse events as described in Table 14-13.

Any dose change must be recorded on the respective Dosage Administration Record CRF.

14.11.2 Dose modifications for patients from protocol SOM230B2305

For patients who are unable to tolerate the protocol-specified dose level, dose adjustments are permitted in order to keep the patient on study drug. (Refer to Table 14-13). At any time during the study, patients with an early morning (between 8 and 10am) serum cortisol < 3 µg/dl and a UFC measurement < LLN or symptoms suggestive of hypoadrenalism (e.g. postural hypotension, nausea, and abdominal pain) and a UFC measurement <LLN should have their dose reduced.

During the roll-over, the investigator may reduce the dose in 300 µg s.c. b.i.d. steps at any time if the patient does not tolerate the given pasireotide dose. The minimum dose to be administered will be 300 µg s.c. b.i.d.. If the patient does not tolerate the 300 µg s.c. b.i.d. dose, he/she will be withdrawn from the study.

These changes must be recorded on the Dosage Administration Record.

Table 14-13 Dose modification for AEs, excluding LFT increase, QT prolongation and hyperglycemia

Adverse event	Action
CTCAE grade ≤ 2	No drug adjustments
CTCAE grade ≥ 3 and assessed as study drug related	Reduce pasireotide to the next dose level. If the AE improves to grade ≤ 2 before the next administration, increase dose back to the prior dose. If the dose is increased and the AE recurs at a grade ≥ 3, the dose should be reduced again. The patient should stay on this lower dose and no further dose titrations are allowed. If the AE does not improve to grade ≤ 2, the dose is to be reduced further. If the AE does not improve to grade ≤ 2 on the minimum study dose, the treatment should be stopped. The patient should be discontinued and followed up for safety.
For the management of LFT increase, QT prolongation, and hyperglycemia refer to specific instructions provided in Appendix 2, Appendix 3 and Appendix 4.	

14.12 Appendix 12: Dose modification information for patients with Cushing's receiving pasireotide s.c in combination with cabergoline (SOM230B2411)

Table 14-14 Dose and treatment schedule

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

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

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

If the 0.9mg twice a day dose is not tolerated and biochemical control is not achieved, patient will begin combination treatment of pasireotide at 0.6mg twice a day plus cabergoline at 0.5mg once a day for 8 weeks. If during or at the end of the 8-week period, the biochemical control is not achieved, the combination dose will be increased to pasireotide at 0.6mg twice a day plus cabergoline at 1.0mg once a day for 8 weeks. The patient will continue with the highest combination dose of 0.6mg pasireotide twice a day plus 1.0mg cabergoline once a day, or 0.9mg pasireotide twice a day plus 1.0mg of cabergoline once a day for 8 weeks. (see Table 14-15)

If patient does not tolerate 0.6mg twice a day, the dose of pasireotide should be decreased to 0.3mg twice a day. If pasireotide 0.3mg twice a day does not lead to biochemical control after at least 8 weeks of treatment, combination with cabergoline as described above can be initiated (see Table 14-15).

If patient cannot increase from 0.6mg twice a day to 0.9mg twice a day due to safety, and is not yet biochemically controlled, combination with cabergoline 0.5mg qd can be initiated right away with pasireotide at 0.6mg twice a day (see Table 14-15).

If patient is being escalated to 0.9mg twice a day, but cannot tolerate the dose, dose should be reduced to 0.6mg twice a day. If the latter dose does not lead to biochemical control, combination with cabergoline as described above can be initiated (see Table 14-15).

If combination pasireotide and cabergoline 0.5mg once a day is not tolerated, the dose of cabergoline can be reduced to 0.5mg every other day. If 0.5mg every other day is not tolerated, and biochemical control is not achieved, patient should be considered for discontinuation if no clinical benefit is derived (see Table 14-15).

If combination pasireotide and cabergoline 1.0mg once a day is not tolerated, the dose of cabergoline can be reduced to 1.0mg every other day. If 1.0mg every other day is not tolerated, and biochemical control is not achieved, patient should be considered for discontinuation if no clinical benefit is derived (see Table 14-15).

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

Table 14-15 Pasireotide and cabergoline dose modification steps for pasireotide un-treated patients

Pasireotide: pasi Cabergoline: cabe	Starting dose level	Dose modification level – 1	Dose modification level – 2	Dose modification level - 3	Dose medication level - 4
Modification # 1	0.6mg bid pasi[a]	0.3mg bid pasi[b]	0.3mg bid pasi + 0.5mg cabe qd[b]	0.3mg bid pasi + 1.0mg cabe qd	
Modification # 2	0.6mg bid pasi[b]	0.9mg bid pasi[b]	0.9mg bid pasi + 0.5mg qd cabe[b]	0.9mg bid pasi + 1.0mg qd cabe	
Modification # 3	0.6mg bid pasi[b]	0.9mg bid pasi[a]	0.6mg bid pasi[b]	0.6mg bid pasi + 0.5mg cabe qd[b]	0.6mg bid pasi + 1.0mg cabe qd
Modification # 4	0.6mg bid pasi[c]	0.6mg bid pasi + 0.5mg qd cabe[b]	0.6mg bid pasi + 1.0mg cabe qd		
Modification # 5	0.9mg bid pasi[ab]	0.6mg bid pasi + 0.5mg qd cabe[b]	0.6mg bid pasi + 1.0mg qd cabe		
Modification # 6	0.3, 0.6 or 0.9mg bid pasi + 0.5mg qd cabe[a]	0.3, 0.6 or 0.9mg bid pasi + 0.5mg every other day cabe[ab]	Discontinuation if no clinical benefit		
Modification # 7	0.3, 0.6 or 0.9mg bid pasi + 1.0mg qd cabe[a]	0.3, 0.6 or 0.9 mg bid pasi + 1.0mg every other day cabe[ab]	Discontinuation if no clinical benefit		

[a]Dose modification is initiated if the current dose is not tolerated
[b]Dose modification is initiated if biochemical control is not achieved
[c]Dose cannot be increased to the next level due to toxicity but biochemical control is not achieved

Patients currently treated with maximal tolerated doses of pasireotide monotherapy: 0.3mg bid, 0.6mg bid or 0.9mg bid, for at least 8 weeks but did not achieve biochemical control will begin their combination treatment of pasireotide at 0.3mg, 0.6mg or 0.9mg bid plus 0.5mg of cabergoline once a day at study entry. They will continue the treatment for 8 weeks. If

biochemical control is not achieved at the end of the 8-week period, the dose of cabergoline will be increased to 1.0mg once a day and continue with the combination treatment for the remainder of study treatment.

If combination pasireotide and cabergoline 0.5mg once a day is not tolerated, the dose of cabergoline can be reduced to 0.5mg every other day. If 0.5mg every other day is not tolerated, and biochemical control is not achieved, patient should be considered for discontinuation if no clinical benefit is derived (see Table 14-16).

If combination pasireotide and cabergoline 1.0mg once a day is not tolerated, the dose of cabergoline can be reduced to 1.0mg every other day. If 1.0mg every other day is not tolerated, and biochemical control is not achieved, patient should be considered for discontinuation if no clinical benefit is derived (see Table 14-16).

The minimum treatment of any regimen is 8 weeks. Patients losing biochemical control at any time point after the 8-week treatment period at the starting combination dose will have the dose of the study mediation increased immediately to the next level provided that the dose is well tolerated (see Table 14-16).

Table 14-16 Pasireotide and cabergoline dose modification steps for patients currently treated with maximal tolerated doses of pasireotide monotherapy

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

[a]Dose modification is initiated if the current dose is not tolerated
[b]Dose modification is initiated if biochemical control is not achieved