

Clinical Development

Pasireotide LAR / SOM230 LAR

Oncology Clinical Trial Protocol CSOM230C1202 / NCT01673646

A multicenter, open-label, randomized, phase II study to evaluate efficacy, safety, pharmacokinetics and pharmacodynamics of pasireotide LAR in Japanese patients with active acromegaly or pituitary gigantism

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List of abbreviations

| | |
|---------|---|
| ACTH | Adrenocorticotrophic Hormone |
| ADA | American Diabetes Association |
| AE | Adverse Event |
| Alb | Albumin |
| ALP | alkaline phosphatase |
| ALT | Alanine aminotransferase/glutamic pyruvic transaminase/GPT |
| ANA | Anti-nuclear antibody |
| APTT | Partial thromboplastin time |
| AST | Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT |
| ATC | Anatomical therapeutic chemical |
| AUC | area under the drug plasma (serum/blood) concentration-time curve |
| AUCinf | area under the drug plasma (serum/blood) concentration-time curve (time 0 to infinity) |
| AUClast | area under the drug plasma (serum/blood) concentration-time curve (time 0 to the last measurable concentration sampling time) |
| b.i.d. | bis in diem/twice a day |
| BMI | body mass index |
| BUN | Blood urea nitrogen |
| Cmax | maximal drug plasma (serum/blood) concentration |
| CMH | Cochran-Mantel-Haenszel |
| CMV | Cytomegalovirus |
| CPK | Creatine phosphokinase |
| CRF | Case Report/Record Form |
| CRO | Contract research organization |
| CSR | Clinical study report |
| CTCAE | Common Toxicity Criteria for Adverse Events |
| Ctrough | trough drug plasma (serum/blood) concentration |
| CV | Coefficient of variation |
| DM | Diabetes Mellitus |
| DPP-4 | dipeptidyl peptidase-IV |
| DS&E | Drug safety and Epidemiology |
| EBV | Epstein-Barr Virus |
| ECG | Electrocardiogram |
| EDC | Electronic data capture |
| FAS | Full analysis set |
| FPG | Fasting Plasma Glucose |
| GCP | Good Clinical Practices |
| GEP/NET | Gastroenteropancreatic neuroendocrine tumor |
| GGT | Gamma-glutamyltransferase |
| GH | Growth Hormone |
| GI | Gastrointestinal |
| GIP | glucose dependent insulintropic polypeptide, also known as gastric inhibitory polypeptide |
| GLP-1 | glucagon-like peptide-1 |
| HAV | Hepatitis A virus |
| HbA1c | hemoglobin A1c |
| HBc | Hepatitis B core |

| | |
|---------|---|
| HBsAg | Hepatitis B surface antigen |
| hCG-β | Human chorionic gonadotropin, β-subunit |
| HCV | Hepatitis C virus |
| HDL | High density lipoprotein |
| HEV | Hepatitis E virus |
| Hgb | hemoglobin |
| hsst | Human somatostatin subtype receptor |
| i.m. | intramuscular |
| ICF | Informed consent form |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |
| IGF-1 | Insulin-like Growth Factor-1 |
| IgM | Immunoglobulin M |
| IRB | Institutional Review Board |
| LAR | Long Acting Release |
| LDH | Lactic dehydrogenase |
| LDL | Low density lipoprotein |
| LFT | Liver function test(s) |
| LLN | Lower limit normal |
| MAP | Master Analysis Plan documents project standards in the statistical methods which will be used within the individual clinical trial RAP documentation |
| MedDRA | Medical Dictionary for Drug Regulatory Activities |
| MRI | Magnetic Resonance Imaging |
| NCI-CTC | National Cancer Institute-common toxicity criteria |
| NYHA | New York Heart Association |
| OGTT | Oral Glucose Tolerance Test |
| PAS | Pharmacokinetic analysis set |
| PHI | Protected health information |
| PK/PD | Pharmacokinetic/Pharmacodynamic |
| PLT | Platelet count |
| PPS | Per protocol set |
| PRL | Prolactin |
| PT | Prothrombin time |
| q.d. | Once a day |
| QOL | Quality of life |
| RAP | The report and analysis plan |
| RBC | Red blood cell counts (erythrocyte counts) |
| REB | Research Ethics Board |
| s.c. | Subcutaneous |
| SAE | Serious Adverse Event |
| SD | Standard deviation |
| SEC | Safety event categories |
| SGOT | Serum glutamic oxaloacetic transaminase |
| SGPT | Serum glutamic pyruvic transaminase |
| SSA | Somatostatin analogues |
| SST | Somatostatin |
| SSTR | Somatostatin Receptor |

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|-----|--|
| T4 | Thyroxine |
| TSH | Thyroid Stimulating Hormone |
| ULN | Upper Limit Normal |
| VT | Ventricular Tachycardia |
| WBC | White blood cell counts (leukocyte counts) |
| WHO | World Health Organization |

Glossary of terms

| | |
|---------------------------------|---|
| Assessment | A procedure used to generate data required by the study |
| Enrollment | Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol) |
| Investigational drug | The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug.” |
| Patient Number | A unique identifying number assigned to each patient who enrolls in the study |
| 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. |
| Stage related to study timeline | A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of study treatment, etc. |
| Stop study participation | Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later |
| Study treatment | Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational study treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational study treatments in combination. |
| Study treatment discontinuation | Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal |
| Variable | Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints |

Amendment 3

Amendment rationale

As of May 31 2014, patient enrollment has been completed and 33 patients have been randomized in this trial.

The purpose of this amendment is to update [Table 7-2](#) to clarify what assessments need to be performed in patients that remain in the study for more than 2 years of treatment.

This amendment will introduce the following change to the study protocol:

Update Table 7-2 to clarify assessments beyond 2 years of treatment

The protocol allows patients to continue study drug until it becomes commercially available or until pasireotide LAR development program is discontinued. No information regarding the assessments to be performed in patients in the study beyond 2 years of treatment had been included in the Visit schedule. [Table 7-2](#) has been updated to include pregnancy assessment and collection of adverse events for patients in the study beyond 2 years of treatment.

Changes to the protocol

- Change to [Table 7-2](#): Table 7-2 “Extension Visit evaluation schedule” has been updated for patients who continue the study treatment beyond 2 years.

IRB/IEC/REB Approval

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

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

Amendment 2

Amendment rationale

As of Aug 31, 2013, 8 patients have been randomized to receive treatment in this trial.

Additional insights gained from recent analysis of pasireotide s.c. data and feedback received from study investigators resulted in amending or clarifying sections within the study protocol with the aim to facilitate recruitment. This amendment will introduce the following changes to the study protocol:

1. Allow patients previously or current treated with GH receptor antagonists to be enrolled
2. Reduce the exclusion period after radiotherapy from ten years to three years
3. Reduce the study visit
4. Provide guidance for blood glucose monitoring and management of hyperglycemia
5. Provide more updated pregnancy guidelines
6. Introduce changes to the biomarker analysis

The rationale for these changes is presented below:

Include Patients who have been treated with GH receptor antagonists during the last 8 weeks prior to Visit 1:

In clinical practice, many patients who have inadequately controlled acromegaly or pituitary gigantism have been treated with the combination therapy of GH receptor antagonists and somatostatin analogues (SSA). The objective of the combination therapy is that GH receptor antagonist normalizes IGF-1 and SSA controls GH value. The results of SOM230C2305 shows that pasireotide LAR is more effective than SSA (octreotide LAR) in IGF-1 control rate. Pasireotide LAR has the potential to normalize IGF-1 and control GH in patients who have been treated with GH receptor antagonists. Therefore, patients who have been treated with GH antagonists can be enrolled in CSOM230C1202.

Reduce the exclusion period after radiotherapy from ten years to three years

In case of conventional fractionated radiotherapy, the mean time to remission after conventional RT is about 10 years. Recently, stereotactic radiotherapy is utilized and this type of radiotherapy, it takes about 3 years to gain GH and IGF-1 normalization.

Change of the visit schedule:

The enrollment of patients in this trial is quite slow and one of the causes for the slow enrollment is the high frequency of study visits to the investigational site. Non-critical PK and PD sampling has been removed to decrease the patient burden.

Management of Hyperglycemia:

The management of hyperglycemia has been expanded. This is done to reinforce glycemic goals of treatment per current ADA and EASD guidelines and to emphasize the need to initiate anti-hyperglycemic treatment accordingly when needed.

Update to Pregnancy Guidelines:

Considering pasireotide LAR half-life of 15.74 days, this amendment mandates female or male patients to continue preventive pregnancy procedures (i.e. use of oral contraception, use of condoms respectively) for three months post last pasireotide LAR dose (instead of two months). In addition follow up of a newborn of a patient or a partner who becomes pregnant during the study has been added (3months post-delivery).

Biomarkers analysis:

- Based on the experiences in other pasireotide studies, the few paraffin embedded tissue samples obtained will be used to determine the expression of SSTR1-5 receptors by immunohistochemistry (IHC) method and not by PCR method. Therefore mentioning of the PCR methodology was deleted.
- The small number of tissue samples obtained is too low for adequate analysis of Gs alpha mutation and that has therefore been deleted.
- In addition, determination of Ki67 would be most valuable in a study in which tumor biopsies from pre- and post-treatment would be available. As pituitary samples from patients cannot and will not be determined after treatment and only very few samples may be obtained from historical samples in this trial, the analysis of the expected few cases is not meaningful and will be deleted.

Clarification/Inconsistencies:

Clarification was provided through edited text and inconsistent language was corrected throughout the protocol.

- The exclusion criterion 15 was corrected to clarify the exclusion of patients that have either chronic or active hepatitis B or C.
- The footnote for AE Table 6-2 was revised to refer to the specific management for QT prolongation and LFT increases provided in anticipated risks and safety concerns of the study drug Section 6.3.3.
- The criterion listed for patient withdrawal based on capillary glucose values in excess of 275 mg/dL (15.5 mmol/L) which was erroneously added previously has been removed. (Section 7.1.3.1)

Changes to the protocol

- Changes to the Table of contents: current page numbers and changes to section headings.
- Change to Protocol Summary: Changes in the main body of the protocol (see bullet points below) are also implemented in the relevant sections of the protocol synopsis.
- Changes to Section 5.3:
 - Exclusion criteria 1: Changed 3rd bullet to be able to enroll patient who have been treated with GH antagonists.
 - Exclusion criteria 7: Reduced the exclusion period after radiotherapy from ten years to three years prior to visit 1.

- Exclusion criteria 15: Removed “and” and replaced it with “or” for the type of chronic viral hepatitis.
- Exclusion criteria 20: Extended the contraception period after the last dose from 2 months to 3 months
- Change to Figure 6-1: Modified Figure 6-1 by adding “obtain fasting plasma glucose”
- Change to Table 6-2: Footnote corrected to “For the management of QT prolongation and LFT increases refer to specific instructions provided in Section 6.3.3 Anticipated risks and safety concerns of the study drug (Figure 6-2 and Figure 6-3)”.
- Changes to Section 6.3.3: Sub-heading and information was added to reflect guidance on the monitoring of blood glucose
- Changes to Section 6.4.1: Extended the contraception period after the last dose from 2 months to 3 months.
- Change to Table 7-1: Removed the visit number 3, 4 and 7.
- Change to Table 7-3: Removed the descriptions of day 2, 15 and 43.
- Change to Table 7-5: Removed the visit number 3, 4 and 7
- Change to Section 7.2.4: Deletion of the PCR methodology and analysis of Ki67 and Gs alpha mutation.
- Change to Section 8.3: Added language related to follow up of a newborn of a patient or a partner who becomes pregnant during the study (3 months post-delivery).
- Change to Section 10.6.1: Added description of “Different Analysis may be applied for patients before and after Amendment 2”.

IRB/IEC/REB Approval

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

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

Amendment 1

Amendment rationale

As of July 15, 2012 study CSOM230C1202 has not been initiated at any study center and no patients has received study drug in the trial.

The purpose of this amendment is to revise the randomization number and to make the editorial changes throughout the protocol.

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.

- Changes to Section 1.1: Clarified disease
- Changes to the List of abbreviations: Deleted LOCF
- Change to Section 5.2: Added dopamine agonists to Inclusion 3b to consist with the definition of prior medications
- Changes to Section 6.4.3: Clarified the criteria
- Changes to Section 6.5.2.1 and Table 6-4: Revised the randomization numbers for either with prior medication or without prior medication
- Changes to Table 7-1 and Table 7-2: Added pituitary gigantism to History of acromegaly, Prior therapy for acromegaly and Symptom of Acromegaly where applicable
- Changes to Section 7.1.1.3: Clarified disease
- Changes to Section 7.2.1.4: Clarified disease
- Changes to Section 8.2.2: Corrected to remove language 'in English' regarding to completing SAE report form
- Changes to Section 11.2: Corrected the language that follow the Japanese regulation.

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.

Protocol summary:

| | |
|--|--|
| Protocol number | CSOM230C1202 |
| Title | A multicenter, open-label, randomized, phase II study to evaluate efficacy, safety, pharmacokinetics and pharmacodynamics of pasireotide LAR in Japanese patients with active acromegaly or pituitary gigantism |
| Brief title | Evaluate Efficacy and Safety of pasireotide LAR in patients with active acromegaly |
| Sponsor and Clinical Phase | Novartis, Phase II |
| Investigation type | Drug |
| Study type | Interventional |
| Purpose and rationale | <p>Pasireotide LAR was tested in patients with acromegaly in phase I patient study [CSOM230C2110]. Patients in this study received once every 28 days doses of 20, 40 or 60 mg pasireotide LAR, given as an i.m. depot intragluteal injection for a period of 3 months.</p> <p>The response rate, the proportion of patients with a reduction of 5-point mean GH levels to <2.5 µg/L and normalization of IGF-1 to within normal limits (age and sex related), at 3 months of study treatment was 30% in the 20 mg group, 41.7% in the 40 mg group, and 38.5% in the 60 mg group.</p> <p>The phase 3 study [CSOM230C2305] demonstrated Pasireotide LAR was superior in efficacy [i.e. GH levels to <2.5 µg/L and normalization of IGF-1 to within normal limits (age and sex related)] to octreotide LAR for patients with medication naive active acromegaly. Pasireotide LAR appeared to have a similar safety profile relative to octreotide LAR, except for hyperglycemia (Section 1.2.1.2). Pasireotide LAR was generally tolerated in Japanese healthy volunteers from the tested doses (10-60 mg) [CSOM230G1101]. And the safety profile in Japanese healthy volunteers was similar to that in Western healthy volunteers [CSOM230C2101].</p> <p>Basically, acromegaly and pituitary gigantism are identical diseases. Pituitary gigantism is also caused by a GH-secreting pituitary adenoma. According to the guidance of diagnosis and treatment for these diseases, major symptoms of pituitary gigantism are almost same as acromegaly and treatment strategy is same as acromegaly. Therefore it is expected that pasireotide has efficacy for not only acromegaly but also pituitary gigantism.</p> <p>The purpose of [CSOM230C1202] is to evaluate the efficacy, safety, pharmacokinetics and pharmacodynamics of pasireotide LAR in Japanese patients with acromegaly and pituitary gigantism.</p> |
| Primary Objective(s) and Key Secondary Objective | <p>Primary objective: Assess the total-group efficacy of pasireotide LAR on the reduction of mean GH levels to < 2.5 µg/L and the normalization of IGF-1 at 3 months of study treatment</p> <p>Key Secondary Objective:</p> <ul style="list-style-type: none"> ● Assess the effect of each starting dose pasireotide LAR on the reduction of mean GH levels to < 2.5 µg/L and the normalization of IGF-1 at 3 months of study treatment ● Assess the PK and PK/PD of pasireotide LAR 20 mg, 40 mg and 60 mg ● Assess the tolerability and safety profile of pasireotide LAR at 3 months and during and after the 12- month study treatment ● Assess the effect of pasireotide LAR on the reduction of mean GH levels to < 2.5 µg/L at 3 months of study treatment ● Assess the effect of pasireotide LAR on the normalization of IGF-1 at 3 months of study treatment |

| | |
|-----------------------------|---|
| <p>Secondary Objectives</p> | <p>Core phase Objective 1: Assess the effect of pasireotide LAR on the reduction of mean GH levels to < 2.5 µg/L and the normalization of IGF-1 at 6, 9 and 12 months of study treatment Objective 2: Assess the effect of pasireotide LAR on the reduction of mean GH levels to < 2.5 µg/L at 6, 9 and 12 months of study treatment Objective 3: Assess the effect of pasireotide LAR on the normalization of IGF-1 at 6, 9 and 12 months of study treatment Objective 4: Assess the effect of pasireotide LAR on the change of tumor volume at 6 and 12 months of study treatment Objective 5: Assess the effect of pasireotide LAR on the change of mean GH level from baseline Objective 6: Assess the effect of pasireotide LAR on the symptoms of acromegaly, specifically: ring size, headache, fatigue, perspiration, paresthesias, osteoarthralgia Objective 7: Assess the effect of pasireotide LAR on the change of prolactin (PRL) level from baseline Extension phase Objective 1: Assess the effect of pasireotide LAR as long term study treatment on the proportion of patients with a reduction of mean GH level to < 2.5 µg/L and normalization of IGF-1 at 18 and 24 months of study treatment Objective 2: Assess the effect of pasireotide LAR as long term study treatment on the reduction of mean GH levels to < 2.5 µg/L at 18 and 24 months of study treatment Objective 3: Assess the effect of pasireotide LAR as long term study treatment on the normalization of IGF-1 at 18 and 24 months of study treatment Objective 4: Assess the effect of pasireotide LAR as long term study treatment on the change of mean GH levels from baseline Objective 5: Assess the safety and tolerability of pasireotide LAR in extension phase Objective 6: Assess the total-group safety and tolerability of pasireotide LAR as long term study treatment</p> |
| <p>Study design</p> | <p>A multicenter, open-label, randomized study. This study consists of two phases, core phase and extension phase. Patients will be treated with SOM230 LAR for 12 months in the core phase. The patients will be randomized to one of 3 doses (20mg, 40mg or 60mg).</p> |
| <p>Population</p> | <p>Adult (at least 18 years of age), male and female patients, with medication naïve acromegaly and pituitary gigantism or inadequately controlled acromegaly and pituitary gigantism with current medications. 30 patients will be enrolled.</p> |
| <p>Inclusion criteria</p> | <ol style="list-style-type: none"> 1. Written informed consent obtained prior to any screening procedures 2. Male or female patients of at least 18 years of age 3. Patients with active acromegaly or pituitary gigantism following a or b <ol style="list-style-type: none"> a. Patients with medication naïve acromegaly or pituitary gigantism demonstrated by: <ul style="list-style-type: none"> • a lack of suppression of GH nadir to <1 µg/L after an oral tolerance test with 75 g of glucose (OGTT) (not applicable for diabetic patients) or a mean GH concentration of a 5-point profile within a 2 hour time period of > 5 µg/L • elevated circulating IGF-1 concentration (age and sex related) • Patients who have undergone one or more pituitary surgeries, but have not been treated medically or de-novo patients presenting a visible pituitary adenoma on MRI and who refuse pituitary surgery or for whom pituitary surgery is contraindicated b. Patients with inadequately controlled acromegaly or pituitary gigantism as defined by a mean GH concentration of a 5- point profile over a 2-hour period > 2.5 µg/L and age and sex related IGF-1 > 1.3 x upper limit of laboratory normal (ULN), even if acromegaly have been treated for at least 12 weeks with somatostatin analogues or dopamine agonist 4. Patients with a known history or new diagnosis of impaired fasting glucose or diabetes mellitus may be included, however blood glucose and antidiabetic treatment must be monitored closely throughout the trial and adjusted as necessary |

| | |
|---------------------------------------|--|
| Key exclusion criteria | <ul style="list-style-type: none"> ● For patients with inadequately controlled acromegaly or pituitary gigantism with current medication. <ul style="list-style-type: none"> ● Patients who have been treated with dopamine agonists during the last 8 weeks prior to visit 1 (screening). ● Patients who have been treated with long -acting somatostatine analogues during the last 4 weeks prior to visit 1 (screening). ● Patients who have been treated with GH antagonists during the last 8 weeks prior to visit1 (screening). Such patients must have been treated with long -acting somatostatine analogues or dopamine agonists monotherapy continuously for a minimum of 12 weeks prior to starting GH receptor antagonists therapy and they should have been inadequately controlled on monotherapy. ● Diabetic patients whose blood glucose is poorly controlled as evidenced by HbA1c >8% ● Patients who have congestive heart failure (NYHA Class III or IV), unstable angina, sustained ventricular tachycardia, ventricular fibrillation, clinically significant bradycardia, advanced heart block or a history of acute myocardial infarction within the six months preceding enrollment ● Patients with risk factors for torsade de pointes, i.e. patients with a baseline QTcF > 470 ms, hypokalemia, hypomagnesemia, hypocalcemia, family history of long QT syndrome, or patients receiving a concomitant medication known to prolong QT interval. ● Patients with history of liver disease such as cirrhosis, chronic active hepatitis B or C, or patients with ALT or AST more than 2 x ULN, baseline total bilirubin > 1.5 x ULN ● Presence of Hepatitis B surface antigen (HbsAg) ● Presence of Hepatitis C antibody (anti-HCV) ● Female patients who are pregnant or lactating, or are of childbearing potential |
| Investigational and reference therapy | Pasireotide |
| Efficacy assessments | Growth Hormone (GH) glucagon-like peptide-1(IGF-1) Tumor volume Symptoms of acromegaly or pituitary gigantism Prolactin |
| Safety assessments | Adverse Events Laboratory assessments special safety assessments <ul style="list-style-type: none"> ● thyroid ● liver function tests, ● gallbladder examinations ● ECGs |
| Other assessments | Pharmacokinetic(PK) Pharmacodynamic(PD) Biomarker |
| Data analysis | <p>Primary endpoint The overall response rate at 3 months of study treatment along with the corresponding exact 90% confidence interval will be provided. The primary analysis will be performed on the FAS.</p> <p>Key Secondary endpoint The response rate at 3 months of study treatment along with the corresponding exact 95% confidence interval will be provided by dose level at randomization study treatment.</p> <p>Sample size calculation The planned sample size of 30 is determined based on the accuracy of estimated overall response rate at the end of 3 months. Under these assumptions, the sample size of 30 can demonstrate that the lower limit of the exact two-sided 90% CI for the overall response rate is not less than the clinically required minimum response rate.</p> |
| Key words | Pasireotide, acromegaly, Phase II |

1 Background

1.1 Overview of acromegaly and pituitary gigantism pathogenesis, epidemiology and current treatment

Acromegaly and pituitary gigantism are diseases both resulting from excessive secretion of growth hormone (GH) and manifested by characteristic clinical symptoms including enlargement of hands and feet, facial features, as well as metabolic disorders. These symptoms not only disturb daily lives of the patients but also seriously deteriorate their quality of life (QOL). These two diseases are basically common in etiology and study treatment approaches, although distinction is made by the time of disease onset in relation to the closure of the epiphyseal plate: the condition occurring after the closure is called acromegaly, and the condition occurring before the closure is called pituitary gigantism. GH is secreted from the GH secreting cells located in the pituitary anterior lobe, and is responsible for enhancement of bone growth, muscle growth, and control of metabolism. Chronic hypersecretion of GH often leads to heart diseases and cerebrovascular accidents and, if not properly treated, would approximately double or triple the mortality as compared with the general population ([Sherlock et al. 2010](#)) and shorten the life expectation by approximately 10 years ([Rajasooriya et al 1994](#)). 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](#)). According to the 5-year national survey for the period from 1988 to 1992 conducted by the MHW specified disease survey research group for diencephalohypophysial dysfunction (1993), patients with acromegaly amounted to 815 (392 males and 423 females) and those with pituitary gigantism amounted to 28 (21 males and 7 females). The same group ([Saito et al 1991](#)) reported that as of 1989 the estimated average age at disease onset for acromegaly was 35.9 years and the average age at the first diagnosis of acromegaly was 44.5 years, whereas those for pituitary gigantism were 12.6 years and 23.4 years, respectively. In the report, neither prevalence nor incidence of acromegaly per general population in Japan was calculated.

An eleven-year survey for the period from 1995 to 2005 in Miyazaki Prefecture conducted by [Katakami et al \(2006\)](#) estimated the prevalence of acromegaly at 84.6 cases per million people, and the incidence at 5.3 new cases per million annually ([Japan Intractable Diseases Information Center 2009](#)).

The clinical symptoms of acromegaly and pituitary gigantism 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 classified 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 ([Baumann 2001](#)).

The therapeutic goals in acromegaly are to reduce mortality to the expected age and sex related 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 $< 2.5\mu\text{g/L}$ (mean GH concentration of a 5-point profile within a 2-hour time period) or to less than $1\mu\text{g/L}$ after an oral glucose load (Giustina et al 2000). The epidemiological data suggests that the reduction of mean GH levels to $< 2.5\mu\text{g/L}$ improves the mortality rate of acromegalic patients to a level close to that of the general population (Kauppinen-Makelin et al 2005).

Treatment modalities for acromegaly and pituitary gigantism include surgery, drug treatment and radiotherapy.

Surgery: Transphenoidal surgery is currently the most frequently recommended treatment, however the surgical effectiveness varies depending on expertise in pituitary surgery, both the size and extension of the anatomic mass, and the preoperative levels of GH. Surgery is most successful in patients with blood GH levels below $40\mu\text{g/L}$ before the operation and with pituitary tumors no larger than 10 mm in diameter (microadenomas). Approximately 80% of patients with microadenomas and substantially $< 50\%$ of patients with macroadenomas can be effectively treated with surgery. Even when surgery is successful and hormone levels return to normal, patients must be carefully monitored for years for possible recurrence. More commonly, hormone levels may improve, but do not return completely to normal. When patients do not achieve normalization of GH and IGF-1 with surgery they require additional treatment, usually with medication. In addition to the normal risks associated with any surgery, transphenoidal surgery may also result in complications such as cerebrospinal fluid leaks, meningitis, or damage to the surrounding normal pituitary tissue, thus requiring lifelong pituitary hormone replacement.

Radiotherapy: Radiation therapy has been used both as a primary treatment and combined with surgery or medications. Radiotherapy is considered as the treatment choice for patients who have tumor remaining after surgery, for patients who are not good candidates for surgery because of other health problems, and for patients who do not respond adequately to surgery and medication. This treatment generally lowers GH levels for more than 2 year timeframe, although late effects can occur in some cases. Radiation therapy leads to a gradual loss of production of other pituitary hormones with time which can result in the undesired effect of panhypopituitarism. Loss of vision and brain injury, which have been reported, can be complications from radiation treatment. Radiotherapy is not advised as primary treatment, because it may take several years before it is fully effective, and because of its possible complications (Wass et al 2001).

Medical treatment: Currently the medical treatment options for acromegaly include somatostatin analogues, growth hormone antagonists and dopamine agonists.

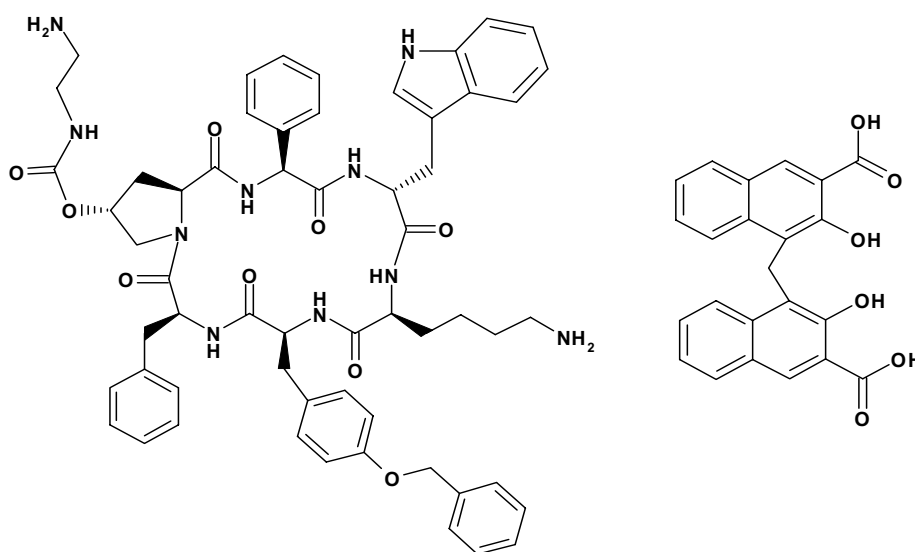
Somatostatin analogues (SSA) have been proven to be safe, well-tolerated and effective and are the medical treatment of choice for acromegalic patients. The currently marketed SSAs are octreotide (Sandostatin[®], Sandostatin[®]LAR[®]) and lanreotide (Somatuline[®], not commercially available in Japan). Octreotide has been available for more than 15 years and is considered the world-wide gold standard medical treatment for acromegaly. Other medical treatment options are growth hormone antagonists and dopamine agonists.

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

1.2.1 Overview of pasireotide (SOM230)

Pasireotide (SOM230), a new chemical entity, is an injectable somatostatin analogue. It is a novel cyclohexapeptide containing the amino acids lysine, tryptophane, phenylglycine, aminoethylcarbamoyl-hydroxyproline, phenylalanine and O-benzylytyrosine, with the following structural formulae (Figure 1-1):

Figure 1-1 Pasireotide pamoate structural formulae



Pasireotide (SOM230) contains the structural elements [(2-aminoethyl) amino carbonyl oxy]-L-proline, phenylglycine and tyrosine (benzyl). Like natural somatostatin and other somatostatin analogues (SSA), pasireotide exerts its pharmacological activity via binding to somatostatin receptors (SSTR). There are five known somatostatin receptors: SSTR1, 2, 3, 4 and 5. Somatostatin receptors are expressed in different tissues under normal physiological conditions. Somatostatin analogues activate these receptors with different potencies ([Schmid and Schoeffter 2004](#)) and this activation results in a reduced cellular activity and inhibition of hormone secretion. Somatostatin receptors are strongly expressed in many solid tumors, especially in neuroendocrine tumors where hormones are excessively secreted (e.g. acromegaly ([Freda 2002](#)), GEP/NET tumors ([Oberg 2004](#)) and Cushing's disease ([Van der Hoek et al 2005](#))).

The SSA currently approved for use in the clinic (octreotide and lanreotide: non commercially available in Japan) have a high affinity to the sst subtype 2 (sst2), with moderate or no affinity to the remaining subtypes. Pasireotide exhibits a unique binding profile with high affinity binding to four of the five known human somatostatin receptors (SSTR1, 2, 3 and 5). Compared to octreotide, pasireotide has a binding affinity which is 30-40 times greater for sst1 and sst5 receptors, 5 times greater for sst3 receptors and a comparable affinity for sst2 receptors (see [Table 1-1](#)). A detailed summary of available preclinical data is provided in the [Investigator's Brochure].

Table 1-1 Binding profile for octreotide and pasireotide at hsst1-5 (IC₅₀, M)

| Compound | sst 1 | sst2 | sst3 | sst4 | sst5 |
|---|----------------------|-----------------------|----------------------|-------------------|-----------------------|
| octreotide acetate (SMS 201-995) | 2.8x10 ⁻⁷ | 3.8x10 ⁻¹⁰ | 7.1x10 ⁻⁹ | >10 ⁻⁶ | 6.3x10 ⁻⁹ |
| Pasireotide (SDZ 227-230) | 9.3x10 ⁻⁹ | 1.0x10 ⁻⁹ | 1.5x10 ⁻⁹ | >10 ⁻⁶ | 1.6x10 ⁻¹⁰ |
| Ratio of IC50: octreotide acetate/ pasireotide SMS/SOM230 | 30 | 0.4 | 5 | -- | 40 |

1.2.1.1 Non-clinical experience

Preclinical data on binding affinity and functional activity in vitro and efficacy on hormone secretion in vivo have been obtained with the s.c. formulation in rats, dogs, mice and monkeys. Long-term in vivo studies performed using drug application by osmotic mini-pumps (Bruns 2002, Weckbecker 2002) have shown not only that the inhibitory effect of pasireotide was stronger, but also that there was less response escape (Bruns et al 2002), (Schmid and Silva 2005). Osmotic mini-pumps release a drug substance in a constant, predefined way and thus mimic the constant release pattern of a LAR formulation. Based on the known efficacy of pasireotide on hormone secretion after long-term application, no additional pharmacological experiments with the new LAR formulation are considered necessary.

The PK of pasireotide s.c. in rats and monkeys showed rapid absorption, low clearance, a high volume of distribution, and a half-life (t_{1/2}) suitable for a b.i.d. dosing regimen. The PK of pasireotide LAR in rabbits demonstrated a controlled-release profile suitable for monthly (every 28 days) dosing regimen. In rats, pasireotide was mainly distributed in the liver, kidney, cartilage, lymph nodes and spleen, it was highly metabolically stable, and was found predominantly eliminated as an unchanged form in feces.

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

1.2.1.2 Clinical experience

Pasireotide s.c.

Single doses of pasireotide s.c. up to 1500 µg q.d. and multiple s.c. doses up to 1500 µg q.d., 750 µg b.i.d., and 2100 µg b.i.d., and continuous (7-day) s.c. infusion by a pump, have been well tolerated by healthy volunteers and patients with acromegaly, metastatic carcinoid tumor, or Cushing's disease. The most common adverse events (AEs) were gastrointestinal, predominantly mild diarrhea, nausea, and abdominal pain. These effects were seen at all doses, but occurred more frequently at higher doses in all studies. The frequency of the gastrointestinal events appeared to decrease with time in multiple-dose studies. A number of subjects also reported mild to moderate headaches. Generally events were mild, transient, and only occasionally caused patients to discontinue treatment.

Pasireotide s.c. has been studied in phase II studies at doses of up to 900 µg b.i.d. in acromegalic patients, 1200 µg b.i.d. in patients with CD and patients with carcinoid tumors, with pasireotide s.c. study treatment periods of 4 years, 4.8 years and 1.6 years respectively. For all indications the most frequently reported AEs have been gastrointestinal, predominantly diarrhea, nausea and abdominal pain. Generally these events were mild, transient, and only occasionally caused patients to discontinue study treatment. Pasireotide s.c. has also been evaluated in a Phase III study [CSOM230B2305] in patients with CD. Pasireotide s.c. was well-tolerated. The majority of AEs were consistent with the known adverse drug reactions of SSAs. The most common AEs (incidence $\geq 10\%$) were diarrhea, nausea, abdominal pain, cholelithiasis, hyperglycemia, diabetes mellitus, fatigue and glycosylated hemoglobin increased. Hyperglycemia-related AEs appeared to be the most significant safety concern in terms of frequency of occurrence as well as overall clinical impact (i.e. overall increase in HbA1c of $\sim 1.5\%$ for both dose groups at 6 and 12 months). Hyperglycemia was managed with the addition or adjustment in oral antidiabetic treatment or in some cases the addition of insulin.

Hyperglycemia was also observed across all indications. Blood glucose increases tended to occur with increasing dose, and appeared to be more notable in patients who had a history of hyperglycemia or diabetes mellitus prior to receiving pasireotide s.c.. 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.

There were 3 healthy volunteers who had biochemical changes meeting Hy's Law criteria (i.e. ALT $> 3 \times$ ULN with concurrent total bilirubin $> 2 \times$ ULN, without increases in alkaline phosphatase and no other cause(s) identified for the abnormal findings). One subject received pasireotide 600 µg bid s.c. for 7 days, while the second subject received pasireotide 1950 µg bid s.c. for 5 days. The third subject (pasireotide 600 µg bid s.c. for 7 days) had ALT and total bilirubin increases that met the criteria for Hy's Law but the alkaline phosphatase was not assessed and the subject received a potentially confounding concomitant medication. ALT values for all 3 subjects were greater than $3 \times$ ULN but $< 4 \times$ ULN and total bilirubin values were $< 4 \times$ ULN. All 3 cases were asymptomatic, presented within 10 days after initial pasireotide s.c. administration, and were reversible with discontinuation of pasireotide s.c.. None of the cases were reported as adverse events and the subjects completed the respective studies per protocol. Liver function tests will be monitored during this clinical trial.

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. Detailed information of the results of these two TQT studies can be found in the [Investigator's Brochure].

Pasireotide long acting release (LAR) formulation

A long acting formulation of pasireotide (pasireotide LAR) has been developed to reduce the number of injections from twice a day to once a month in order to enhance convenience and potentially provide a better efficacy profile with a smoother PK profile minimizing fluctuation from C_{max} and C_{min}.

Pasireotide LAR in healthy volunteers

Data from a Western healthy volunteer study [CSOM230C2101] which assessed single i.m. doses of pasireotide LAR up to 60 mg (N=5 per cohort for 40 mg and 60 mg) showed that pasireotide LAR was well-tolerated, and the adverse events (AEs) were comparable with those from octreotide LAR (a long acting release formulation of octreotide). Diarrhea was the most common adverse event which was sometimes associated with abdominal pain and/or flatulence. The gastrointestinal events were mild or moderate in severity. About half of the subjects reported transient mild injection site pain. An increase in fasting blood glucose accompanied by a decrease in fasting blood insulin (and a small decrease in glucagon levels) was observed with the injection of the LAR formulations. Post-prandially, in the LAR formulations there was a marked increase in post-prandial glucose. These changes tended to normalize over time.

Pharmacokinetics (PK) of pasireotide LAR was assessed in healthy volunteers following a single i.m. injection of 40 mg [CSOM230C2101] or 60 mg [CSOM230C2101] [CSOM230C2111]. The PK exposures of pasireotide was dose-proportional with C_{max} of the extended release phase as 9.6 ± 5.1 ng/mL and 15.8 ± 3.3 ng/mL for the 40 and 60 mg doses, respectively [CSOM230C2101]. Multiple-dose PK simulation suggest that this LAR formulation is suitable for monthly (q 28 d) dosing and steady state reaches after three injections.

Further details and data available from the healthy volunteer study [CSOM230C2101] are described in the pasireotide LAR Investigator's Brochure.

Phase I study [CSOM230G1101] is an open-label, single center, dose escalation study to assess the safety, tolerability and PK of single dose of pasireotide LAR in Japanese healthy volunteers. A total of 32 subjects were enrolled, 8 in each of four cohorts. Each cohort received a single dose at 10 mg, 20 mg, 40 mg or 60 mg per subject. The PK analysis demonstrated that exposure of pasireotide (C_{max,p1}, C_{max,p2}, AUC_{last} and AUC_{inf}) increased in a dose-proportional manner (see Figure 1-2 and Table 1-2). No SAE was reported. Most frequently reported adverse events were blood glucose increased (18/32 subjects, 56.3%; 1/8 at 10 mg, 3/8 at 20 mg, 8/8 at 40 mg and 6/8 at 60 mg) and diarrhea (14/32 subjects, 43.8%; 1/8 at 20 mg, 5/8 at 40 mg and 8/8 at 60 mg). Single dose of pasireotide LAR up to 60 mg was in general tolerated among Japanese healthy volunteers.

Figure 1-2 Plasma concentration versus time profiles after a single i.m. administration of pasireotide LAR in Japanese healthy volunteers (PK set) (n=8 each dose cohort) in study CSOM230G1101

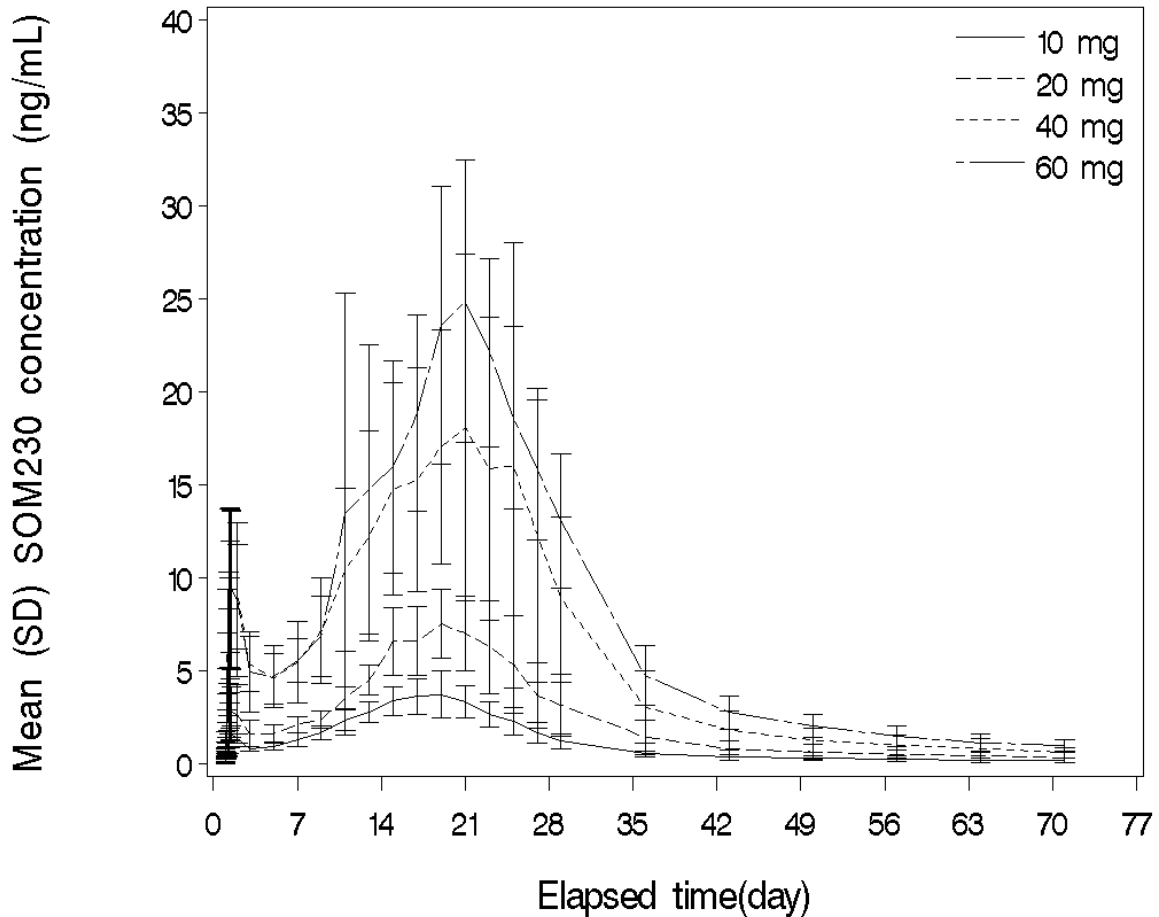


Table 1-2 Summary of PK parameters for pasireotide LAR single dose of 10-60 mg in Japanese healthy volunteers (PK set) in study CSOM230G1101

| | 10 mg N=8 | 20 mg N=8 | 40 mg N=8 | 60 mg N=8 |
|---------------------------|-----------------|------------------|------------------|-------------------|
| Tmax,p1 (hr) | | | | |
| Median | 10.00 | 12.00 | 10.00 | 12.00 |
| Min-Max | 6.0-12.0 | 10.0-24.0 | 8.0-24.0 | 10.0-24.0 |
| Cmax,p1 (ng/mL) | | | | |
| Mean (SD) | 1.703 (0.3740) | 3.110 (1.6296) | 10.551 (4.0629) | 9.726 (4.3778) |
| Tmax,p2 (hr) | | | | |
| Median | 408.0 | 456.0 | 480.0 | 504.0 |
| Min-Max | 336-480 | 336-528 | 384-576 | 240-576 |
| Cmax,p2 (ng/mL) | | | | |
| Mean (SD) | 4.370 (1.0687) | 8.194 (1.6885) | 19.825 (10.3789) | 29.013 (8.9550) |
| AUClast (ng·hr/mL) | | | | |
| Mean (SD) | 1858.9 (246.49) | 3848.0 (1086.89) | 9968.9 (4737.60) | 12840.8 (1349.46) |

| | 10 mg N=8 | 20 mg N=8 | 40 mg N=8 | 60 mg N=8 |
|--------------------------|-----------------|------------------|-------------------|-------------------|
| AUCinf (ng·hr/mL) | | | | |
| Mean (SD) | 1953.1 (271.92) | 4069.3 (1183.95) | 10258.7 (4843.78) | 13394.8 (1467.57) |
| T1/2 (hr) | | | | |
| Mean (SD) | 290.6 (61.84) | 442.9 (253.81) | 341.3 (111.13) | 378.3 (198.59) |
| CL/F (L/hr) | | | | |
| Mean (SD) | 5.204 (0.6900) | 5.240 (1.3024) | 4.468 (1.5157) | 4.526 (0.4883) |
| Vz/F (L) | | | | |
| Mean (SD) | 2167.0 (462.82) | 3292.8 (1738.48) | 2199.1 (1016.81) | 2404.5 (1084.35) |
| MRTlast (hr) | | | | |
| Mean (SD) | 483.1 (42.60) | 518.1 (57.39) | 500.1 (22.44) | 543.7 (61.04) |
| MRTinf (hr) | | | | |
| Mean (SD) | 557.1 (50.12) | 617.1 (108.30) | 549.9 (38.80) | 617.2 (88.24) |

Pasireotide LAR in acromegaly patients

Pasireotide LAR was evaluated in a patient study [CSOM230C2110]. Study [CSOM230C2110] is a multicenter, open-label, randomized study designed to evaluate the pharmacokinetics, safety and tolerability of monthly doses (dosing every 28 days) of 20, 40, and 60 mg pasireotide LAR in patients with acromegaly. Thirty-five acromegaly patients have been enrolled (approximately 10 patients per dose cohort per indication). Preliminary safety data on three months of study treatment reflect a similar safety profile to that observed with pasireotide s.c. Overall, 24 of the 35 patients with acromegaly (68.6%) who received at least one dose of LAR study treatment experienced at least one AE including 7/10 patients in the pasireotide LAR 20 mg group, 7/12 patients in the pasireotide LAR 40 mg group and 10/13 patients in the pasireotide LAR 60 mg group. The most commonly affected primary SOC were Gastrointestinal disorders (13/35 patients; primarily diarrhea), Infections & infestations (12/35 patients; primarily nasopharyngitis), Metabolism & nutrition disorders (9/35 patients; primarily hyperglycemia followed by diabetes mellitus) and Investigations (6/35 patients; primarily blood glucose increased and blood insulin decreased). PK exposures were approximately dose proportional. PK steady state was achieved following 3 injections. PK exposures to pasireotide at steady state in acromegalic patients were comparable to the simulated PK exposures at steady state in healthy volunteers. Further details and data available from the acromegaly patients study [CSOM230C2110] are described in the [pasireotide LAR Investigator's Brochure].

Preliminary data from the Phase III study [CSOM230C2305] assessed the efficacy and safety of pasireotide LAR vs. octreotide LAR in patients with active medication naïve acromegaly. Patients randomized into 40mg pasireotide LAR and 20mg octreotide LAR. Then dose titration was allowed up and down for efficacy and safety reason, respectively. The primary efficacy variable was the proportion of patients with a reduction of mean GH levels to < 2.5µg/L and the normalization of IGF-1 to within normal limits (age and sex related) at 12 months. A two-sided Cochran-Mantel-Haenszel (CMH) test (adjusting for randomization stratification factor) showed a statistical significant result favoring pasireotide LAR (p-value = 0.005). Odds ratio along with 95% confidence interval was 1.992 (1.222, 3.247), response rates and their corresponding confidence intervals were 31.4% (24.5%, 38.7%) and 19.2%

(13.8%, 25.7%) for pasireotide LAR and octreotide LAR, respectively. The response rate at 3 was same as that at 6 months, it was 30.1%. The most frequent AEs were diarrhoea (38.2% and 45.0%), cholelithiasis (25.8% and 37.2%), headache (18.0% and 26.1%), abdominal pain (17.4% and 22.2%), alopecia (18.0% and 19.4%), hyperglycaemia (28.1% and 8.3%), nausea (12.9% and 21.7%), and nasopharyngitis (15.7% and 15.6%) for pasireotide LAR and octreotide LAR. Among the most frequent AEs (>5%), grade 3 or 4 AEs exceeding 2% were hyperglycaemia (2.8% and 0.6%) and diabetes mellitus (5.6% and 0%).

2 Rationale

2.1 Study rationale and purpose

Pasireotide LAR was tested in patients with acromegaly in phase I patient study [CSOM230C2110]. The response rate, the proportion of patients with a reduction of 5-point mean GH levels to <2.5 µg/L and normalization of IGF-1 to within normal limits (age and sex related), at 3 months of study treatment was 30% in the 20 mg group, 41.7% in the 40 mg group, and 38.5% in the 60 mg group.

The phase 3 study CSOM230C2305 demonstrated Pasireotide LAR was superior in efficacy (i.e. GH levels to <2.5 µg/L and normalization of IGF-1 to within normal limits (age and sex related)) to octreotide LAR for patients with medication naive active acromegaly. Pasireotide LAR appeared to have a similar safety profile relative to octreotide LAR, except for hyperglycemia (Section 1.2.1.2). Pasireotide LAR was generally tolerated in Japanese healthy volunteers from the tested doses (10-60 mg) [CSOM230G1101]. The safety profile in Japanese healthy volunteers was similar to that in Western healthy volunteers [CSOM230C2101].

Pituitary gigantism patients are included in the target population. Basically, acromegaly and pituitary gigantism are identical diseases. Pituitary gigantism is also caused by a GH-secreting pituitary adenoma. According to the guidance of diagnosis and treatment for these diseases, major symptoms of pituitary gigantism are almost the same as acromegaly and the treatment strategy is the same as that for acromegaly. Therefore it is expected that pasireotide has efficacy for not only acromegaly but also for pituitary gigantism. The difference between acromegaly and pituitary gigantism from a diagnostic perspective is age at onset. Pituitary gigantism occurs before closing epiphyseal growth plates. However, pituitary gigantism diagnosed in childhood is very rare case. Average age of the initial visit is 23.4 years old. Therefore it is appropriate to include the patient who is at least 18 years of age.

The purpose of [CSOM230C1202] is to evaluate the efficacy, safety, PK and pharmacodynamics of pasireotide LAR in Japanese patients with acromegaly and pituitary gigantism.

2.2 Rationale for the study design

This study is a multi-center, open label, randomized phase II study in Japan evaluating the efficacy, safety, PK and pharmacodynamics of pasireotide LAR in patients with active acromegaly and pituitary gigantism.

With reference to the design of [CSOM230C2110] in western patients with acromegaly, the starting doses of this study will be fixed at 20 mg, 40 mg, and 60 mg during the first 3 months. The response rate is defined as the proportion of responders (responder defined as the reduction of mean GH levels to $< 2.5 \mu\text{g/L}$ and normalization of IGF-1 to within normal limits). The response rates at 20 mg, 40mg and 60mg in [CSOM230C2110] were comparable (30% at 20mg, 41.7% at 40mg, and 38.5% at 60mg). According to [CSOM230C2305], early response was observed at 3 months. And the response rate at 3 months was almost same as that at 6 and 12 months. After 3 months study treatment, the efficacy of pasireotide LAR in overall population will be assessed. As in the case of [CSOM230C2305], it is permitted to increase the dose (up to 60 mg) after the first 3 months of study treatment if biochemical parameters show a mean GH level $\geq 2.5 \mu\text{g/L}$ and/or IGF-1 $> \text{ULN}$ (age and sex related). In the event of any problem with tolerability, it is permitted to reduce the dose down to 20 mg at any time. Core and extension treatment periods were set with reference to [CSOM230C2305].

2.3 Rationale for dose and regimen selection

Pasireotide LAR doses (20mg, 40mg and 60mg) selected for evaluation in this study were based on evaluation of PK, pharmacodynamics, efficacy and safety/tolerability data from patients (acromegaly, carcinoid disease) treated with pasireotide LAR ([CSOM230C2110]) and Japanese healthy volunteers treated with pasireotide LAR ([CSOM230G1101]).

2.4 Rationale for choice of combination drugs

Not applicable.

2.5 Rationale for choice of comparators drugs

Not applicable.

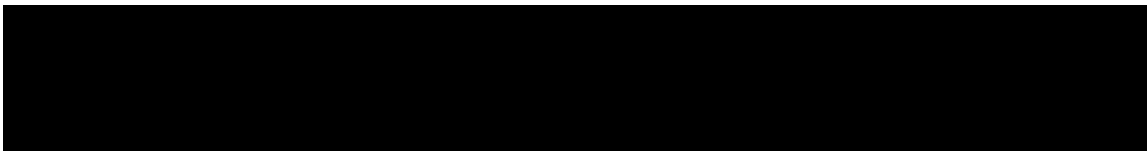
3 Objectives and endpoints

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

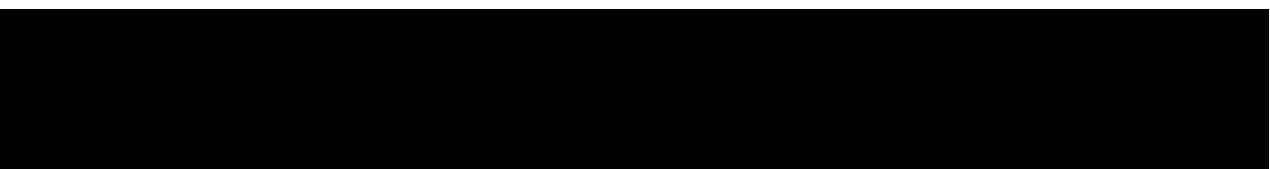
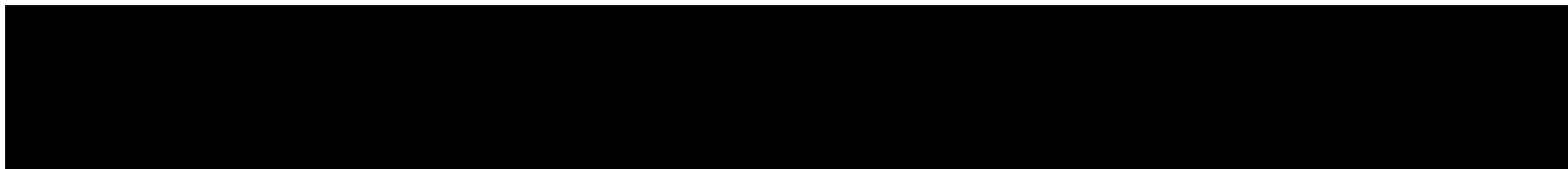
Table 3-1 Objectives and related endpoints

| Objective | Endpoint | Analysis |
|--|--|---|
| Primary | | |
| Assess the total-group efficacy of pasireotide LAR on the reduction of mean GH levels to < 2.5 µg/L and the normalization of IGF-1 at 3 months of study treatment | Proportion of patients with a reduction of mean GH levels to < 2.5 µg/L and the normalization of IGF-1 to within normal limits (age and sex related) at 3 months across all doses | Refer to Section 10.4 |
| Key secondary | | |
| Assess the effect of each starting dose pasireotide LAR on the reduction of mean GH levels to < 2.5 µg/L and the normalization of IGF-1 at 3 months of study treatment | Proportion of patients with a reduction of mean GH levels to < 2.5 µg/L and the normalization of IGF-1 to within normal limits (age and sex related) at 3 months in each starting dose | Refer to Section 10.5.1 |
| Assess the PK and PK/PD of pasireotide LAR 20 mg, 40 mg and 60 mg | PK: C _{trough} , C _{max} , 3 rd inj, accumulation ratio (AR) PD: GH, IGF-1 Safety: blood glucose (BG), HbA1c, ECG, liver function test (LFT) | |
| Assess the tolerability and safety profile of pasireotide LAR at 3 months and during and after the 12- month study treatment | Toxicity will be assessed using the National Cancer Institute-Common Toxicology Criteria (NCI-CTC) grading scale for Adverse Events and for laboratory assessments that include biochemistry, hematology, urinalysis; special safety assessments that include the regular monitoring and recording of blood glucose, HbA1c, thyroid and liver function tests, gallbladder examinations and ECGs. | |
| Assess the effect of pasireotide LAR on the reduction of mean GH levels to < 2.5 µg/L at 3 months of study treatment | Proportion of patients with a reduction of mean GH levels to < 2.5 µg/L at 3 months | |
| Assess the effect of pasireotide LAR on the normalization of IGF-1 at 3 months of study treatment | Proportion of patients with the normalization of IGF-1 to within normal limits (age and sex related) at 3 months | |

| Objective | Endpoint | Analysis |
|---|---|---|
| Other secondary (Core phase) | | Refer to Section 10.5.2 |
| Assess the effect of pasireotide LAR on the reduction of mean GH levels to < 2.5 µg/L and the normalization of IGF-1 at 6, 9 and 12 months of study treatment | Proportion of patients with a reduction of mean GH levels to < 2.5 µg/L and the normalization of IGF-1 to within normal limits (age and sex related) at 6, 9 and 12 months | |
| Assess the effect of pasireotide LAR on the reduction of mean GH levels to < 2.5 µg/L at 6, 9 and 12 months of study treatment | Proportion of patients with a reduction of mean GH levels to < 2.5 µg/L at 6, 9 and 12 months | |
| Assess the effect of pasireotide LAR on the normalization of IGF-1 at 6, 9 and 12 months of study treatment | Proportion of patients with the normalization of IGF-1 to within normal limits (age and sex related) at 6, 9 and 12 months | |
| Assess the effect of pasireotide LAR on the change of tumor volume at 6 and 12 months of study treatment | Change of tumor volume from baseline at 6 and 12 months | |
| Assess the effect of pasireotide LAR on the change of mean GH level from baseline | Change of mean GH levels from baseline | |
| Assess the effect of pasireotide LAR on the symptoms of acromegaly, specifically: ring size, headache, fatigue, perspiration, paresthesias, osteoarthritis | Change of clinical signs from baseline: ring size, headache, fatigue, perspiration, paresthesias, osteoarthritis | |
| Assess the effect of pasireotide LAR on the change of prolactin (PRL) level from baseline | Change PRL level from baseline | |
| Other secondary (Extension phase) | | |
| Assess the effect of pasireotide LAR as long term study treatment on the proportion of patients with a reduction of mean GH level to < 2.5 µg/L and normalization of IGF-1 at 18 and 24 months of study treatment | Proportion of patients with a reduction of mean GH levels to < 2.5 µg/L and the normalization of IGF-1 to within normal limits (age and sex related) at 18 and 24 months of study treatment | |
| Assess the effect of pasireotide LAR as long term study treatment on the reduction of mean GH levels to < 2.5 µg/L at 18 and 24 months of study treatment | Proportion of patients with a reduction of mean GH levels to < 2.5 µg/L at 18 and 24 months of study treatment | |
| Assess the effect of pasireotide LAR as long term study treatment on the normalization of IGF-1 at 18 and 24 months of study treatment | Proportion of patients with the normalization of IGF-1 to within normal limits (age and sex related) at 18 and 24 months of study treatment | |



| Objective | Endpoint | Analysis |
|---|---|-----------------|
| Assess the effect of pasireotide LAR as long term study treatment on the change of mean GH levels from baseline | Change of mean GH levels from baseline in extension phase | |
| Assess the safety and tolerability of pasireotide LAR in extension phase | Toxicity in extension phase will be assessed using the National Cancer Institute-Common Toxicology Criteria (NCI-CTC) grading scale for Adverse Events | |
| Assess the total-group safety and tolerability of pasireotide LAR as long term study treatment | Toxicity in total-group study treatment will be assessed using the National Cancer Institute-Common Toxicology Criteria (NCI-CTC) grading scale for Adverse Events and for laboratory assessments that include biochemistry, hematology, urinalysis; special safety assessments that include the regular monitoring and recording of blood glucose, HbA1c, thyroid and liver function tests, gallbladder examinations and ECGs. | |



4 Study design

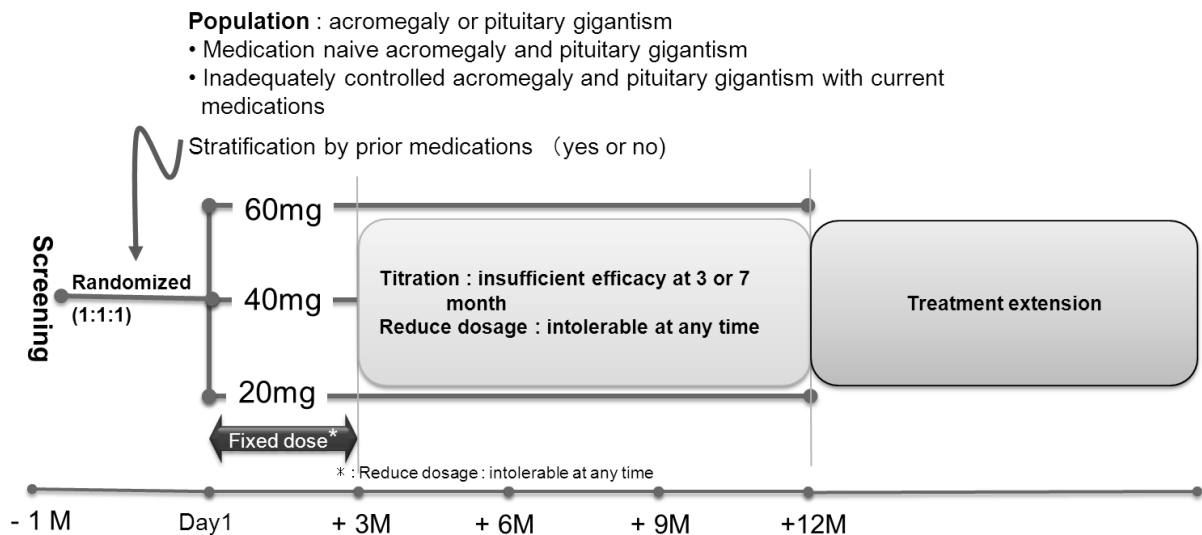
4.1 Description of study design

A total of 30 eligible patients will be enrolled. The enrolled patients will be randomized to one of 3 doses of pasireotide LAR (20 mg, 40 mg, or 60 mg) in a ratio of 1:1:1. Randomization will be stratified by prior medications (e.g. somatostatin analogues, dopamine agonists or GH receptor antagonists), (yes or no). Intramuscular administration of pasireotide LAR will be repeated every month (1 month = 28 days) for 12 months in core phase. It is permitted to increase the dose up to 60 mg in a patient showing the following biochemical test results after 3 and 6 months of study treatment: mean GH levels $\geq 2.5 \mu\text{g/L}$ and/or IGF-1 $> \text{ULN}$ (age and sex related). In the event of any problem with tolerability, it is permitted to reduce the next lower dosage level at any time. After 3 months of study treatment, the primary endpoint (proportion of patients with a reduction of mean GH levels to $< 2.5 \mu\text{g/L}$ and normalization of IGF-1 to within normal limits) will be evaluated.

Patients with a reduction of mean GH levels to $< 2.5 \mu\text{g/L}$ and normalization of IGF-1 at the end of the 12-month study treatment will be enrolled in an extension phase of study treatment. Patients with a mean GH level $\geq 2.5 \mu\text{g/L}$ and/or IGF-1 $> \text{ULN}$ at the end of the 12-month study treatment may be enrolled in an extension phase of study treatment if the extended study treatment is thought to be clinically beneficial for them by the investigator. Patients will receive pasireotide LAR in the extension phase until unacceptable toxicity appears or until the medication is commercially available or until the pasireotide LAR development program is discontinued whichever comes first.

Patients, who participate in the extension phase, will receive a 13th injection of the pasireotide LAR, the Visit 779 (Study completion) will be their last visit.

Figure 4-1 Study design



4.2 Timing of interim analyses and design adaptations

Not applicable

4.3 Definition of end of the study

Completion of the study as a whole (last patient last visit) will occur after all patients have completed all assessments as per [Table 7-1](#) and [Table 7-2](#) (core and extension phase) or have discontinued early.

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in [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 eligible patient population will consist of adult Japanese patients, with active acromegaly or pituitary gigantism.

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

5.2 Inclusion criteria

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

1. Written informed consent obtained prior to any screening procedures
2. Male or female patients of at least 18 years of age
3. Patients with active acromegaly or pituitary gigantism following a or b
 - a. Patients with medication naïve acromegaly or pituitary gigantism demonstrated by:
 - a lack of suppression of GH nadir to <1 $\mu\text{g/L}$ after an oral tolerance test with 75 g of glucose (OGTT) (not applicable for diabetic patients) **or** a mean GH concentration of a 5-point profile within a 2 hour time period of > 5 $\mu\text{g/L}$
 - elevated circulating IGF-1 concentration (age and sex related)
 - Patients who have undergone one or more pituitary surgeries, but have not been treated medically or *de-novo* patients presenting a visible pituitary adenoma on MRI and who refuse pituitary surgery or for whom pituitary surgery is contraindicated

- b. Patients with inadequately controlled acromegaly or pituitary gigantism as defined by a mean GH concentration of a 5- point profile over a 2-hour period $> 2.5 \mu\text{g/L}$ and age and sex related IGF-1 $> 1.3 \times$ upper limit of laboratory normal (ULN), even if acromegaly have been treated for at least 12 weeks with somatostatin analogues or dopamine agonist
4. Patients with a known history or new diagnosis of impaired fasting glucose or diabetes mellitus may be included, however blood glucose and antidiabetic treatment must be monitored closely throughout the trial and adjusted as necessary (see [Section 6.3.3](#))

5.3 Exclusion criteria

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

1. For patients with inadequately controlled acromegaly or pituitary gigantism with current medication.
 - Patients who have been treated with dopamine agonists during the last 8 weeks prior to visit 1 (screening).
 - Patients who have been treated with long -acting somatostatine analogues during the last 4 weeks prior to visit 1 (screening).
 - Patients who have been treated with GH receptor antagonists during the last 8 weeks prior to visit 1 (screening). Such patients must have been treated with long -acting somatostatine analogues or dopamine agonists monotherapy continuously for a minimum of 12 weeks prior to starting GH receptor antagonists therapy and they should have been inadequately controlled on monotherapy.
2. Patients who have received pasireotide (SOM 230) prior to enrollment
3. Patients with compression of the optic chiasm causing any visual field defect for whom surgical intervention is indicated.
4. Patients who require a surgical intervention for relief of any sign or symptom associated with tumor compression
5. Patients who have undergone major surgery/surgical therapy for any cause within 4 weeks of visit 1
6. Patients who have received radiotherapy (except for pituitary irradiation) for any reason in the 4 weeks prior to visit 1 must have recovered from any side effect of radiotherapy
7. Patients who have received pituitary irradiation within the last three years prior to visit 1
8. Patients who are hypothyroid and not adequately treated with stable doses of thyroid hormone replacement therapy
9. Diabetic patients whose blood glucose is poorly controlled as evidenced by HbA1c $>8\%$
10. Patients with symptomatic cholelithiasis
11. Patients with abnormal coagulation (PT and/or APTT elevated by 30% above normal limits) or patients receiving anticoagulants that affect PT (prothrombin time) or APTT (activated partial thromboplastin time)
12. Patients who have congestive heart failure (NYHA Class III or IV), unstable angina, sustained ventricular tachycardia, ventricular fibrillation, clinically significant bradycardia, advanced heart block or a history of acute myocardial infarction within the six months preceding enrollment

13. Patients with risk factors for torsade de pointes, i.e. patients with a baseline QTcF > 470 ms, hypokalemia, hypomagnesemia, hypocalcemia, family history of long QT syndrome, or patients receiving a concomitant medication known to prolong QT interval.
14. Patients with confirmed central hypothyroidism, central hypoadrenalism and diabetes insipidus, unless they are adequately treated with stable doses of hormone replacement therapy for a minimum of three months prior to study entry (first dose of study medication). Patients with confirmed central hypogonadism unless they are adequately treated with stable doses of hormone replacement therapy for a minimum of three months prior to study entry (first dose of study medication) except in cases where hormones replacement therapy is not indicated.
15. Patients with history of liver disease such as cirrhosis, chronic active hepatitis B or C, or patients with ALT or AST more than 2 x ULN, baseline total bilirubin > 1.5 x ULN
16. Presence of Hepatitis B surface antigen (HbsAg)
17. Presence of Hepatitis C antibody (anti-HCV)
18. Patients with WBC <3 x 10⁹/L; Hgb < 90 % LLN; PLT <100 x 10⁹/L
19. Patients who have any current or prior medical condition that may interfere with the conduct of the study or the evaluation of its results in the opinion of the Investigator
20. Female patients who are pregnant or lactating, or are of childbearing potential (defined as all women physiologically capable of becoming pregnant) and not practicing an effective method of contraception/birth control. Female patients of child bearing potential and sexually active males must use a condom during intercourse while taking the drug and for 3 months after the last dose of study drug 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. Effective contraception methods include:
 - Use of oral, injected or implanted hormonal methods of contraception
 - Placement of an intrauterine device or intrauterine system
 - Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository
 - Total abstinence
 - Patient sterilization (male or female)
21. Patients who have a history of alcohol or drug abuse in the 12 month period prior to receiving pasireotide LAR
22. Patients who have given a blood donation (of 400 ml or more) within 2 months before receiving pasireotide LAR
23. Patients who have participated in any clinical investigation with an investigational drug within 1 month before receiving pasireotide LAR
24. Known hypersensitivity to somatostatin analogues or any components of the LAR formulation
25. Patients with active malignant disease within the last five years (with the exception of basal cell carcinoma or carcinoma in situ of the cervix)
26. Patients with the presence of active or suspected acute or chronic uncontrolled infection

27. Patients with a history of non-compliance to medical regimens or who are considered potentially unreliable or will be unable to complete the entire study
28. Known gallbladder or bile duct disease, acute or chronic pancreatitis

6 Study treatment

6.1 Study treatment

Investigational study treatment: pasireotide LAR i.m.

6.1.1 Dosing regimen

Patient will receive one of three pasireotide LAR i.m. doses of 20, 40, or 60 mg. Intramuscular administration of pasireotide LAR will be repeated every month (1 month = 28 days) for 12 months in core phase. It is permitted to increase the dose up to 60 mg in a patient showing the following biochemical test results after 3 and 6 months of study treatment: mean GH levels ≥ 2.5 $\mu\text{g/L}$ and/or IGF-1 > ULN (age and sex related). In the event of any problem with tolerability, it is permitted to reduce next lower dosage level at any time.

6.1.2 Ancillary treatments

Not applicable.

6.1.3 Rescue medication

Not applicable.

6.1.4 Guidelines for continuation of treatment

Patients may continue treatment provided no tolerability issues are present (See [Section 6.3](#)) and criteria for discontinuation are not met (see [Section 7.1.3](#)).

6.1.5 Treatment duration

Patients will be treated for 12 months in the core phase of the study and will have the option to continue study treatment for 12 more months in the extension phase of the study.

6.2 Dose escalation guidelines

Not applicable.

6.3 Dose modifications

6.3.1 Dose modification and dose delay

Dose up-titration

Dose increases is permitted after the first three months of treatment (steady-state reached) if biochemical parameters show a mean GH level ≥ 2.5 $\mu\text{g/L}$ and/or IGF-1 $>$ ULN (age and sex related) and there are no tolerability issues (see [Table 6-1](#)). Patients on the 20 mg arm with a mean GH level ≥ 2.5 $\mu\text{g/L}$ and/or IGF-1 $>$ ULN (age and sex related) after the Month 2.75 (Visit 11) GH and IGF-1 assessment will have their dose increased to 40 mg at Month 3 (Visit 12), if there are no tolerability issues. Patients on the 40 mg arm with a mean GH level ≥ 2.5 $\mu\text{g/L}$ and/or IGF-1 $>$ ULN (age and sex related) after the Month 2.75 (Visit 11) GH and IGF-1 assessment will have their dose increased to 60 mg at Month 3 (Visit 12), if there are no tolerability issues. At Month 7 (Visit 16), patients receiving 20 mg and 40 mg doses with mean GH level ≥ 2.5 $\mu\text{g/L}$ and/or IGF-1 $>$ ULN (age and sex related) after the Month 6 (Visit 15) GH and IGF-1 assessment will have their dose increased to 40 mg and 60 mg, respectively, if there are no tolerability issues. Patients receiving the 60 mg dose at Month 3, 6 or 9 with a mean GH level ≥ 2.5 $\mu\text{g/L}$ and IGF-1 $>$ ULN (age and sex related) will be discontinued from the study unless clinical benefit has been observed as per the investigator's judgment.

Patients that have a mean GH level < 2.5 $\mu\text{g/L}$ and IGF-1 \leq ULN (age and sex related) on current therapy after Month 3 and/or Month 6 will be kept on their current dose.

After Month 12, the timing of the dose adjustments will be based on GH and IGF-1 values, at the investigators discretion but must include duration of at least 3 months on a current dose prior to up-titration and no tolerability issues are present. Patients receiving the 60 mg dose after Month 12 with a mean GH level ≥ 2.5 $\mu\text{g/L}$ and IGF-1 $>$ ULN (age and sex related) will be discontinued from the study unless clinical benefit has been observed as per the investigator's judgment.

Dose down-titration

Dose reduction is due to lack of tolerability (refer to [Table 6-2](#) and [Table 6-3](#)) will be allowed as one dose level reduction at a time (i.e. from 60 mg to 40 mg or from 40 mg to 20 mg) If tolerability issue is resolved, increase dose to that prior to the dose reduction unless investigator opinion to remain on current dose.

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

Dose interruption

If a patients requires a dose interruption of >28 days from the intended day of the next scheduled dose (>56 days from the previous dose), then the patient must be discontinued from the study.

Table 6-1 Dose titration steps for pasireotide LAR

| | Dose level 0 | Dose level 1 | Dose level 2 |
|-----------------------|--------------|-----------------------------|-----------------------------|
| Dose increase | | | |
| SOM230 LAR | 60 mg | Not applicable ¹ | Not applicable ¹ |
| SOM230 LAR | 40 mg | 60 mg | Not applicable ¹ |
| SOM230 LAR | 20 mg | 40 mg | 60 mg |
| Dose reduction | | | |
| SOM230 LAR | 60 mg | 40 mg | 20 mg |
| SOM230 LAR | 40 mg | 20 mg | Not applicable ² |
| SOM230 LAR | 20 mg | Not applicable ² | Not applicable ² |

¹ Dose increase above 60 mg is prohibited.

² Dose reduction below 20mg is prohibited. Dose reduction should be based on the worst toxicity demonstrated at the last dose.

Table 6-2 Guideline for treatment of patients experiencing adverse events

| 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 60 mg to 40mg 40 mg to 20mg 20 mg - 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. If AE does not improve to grade ≤ 2 on the minimum dose the patient will be withdrawn. |

For the management of QT prolongation and LFT increases refer to specific instructions provided in Special Safety in [Section 6.3.3 \(Figure 6-2 and Figure 6-3\)](#).

Table 6-3 Guideline for treatment of patients experiencing adverse events in QTcF

| Adverse event | Action |
|--|--|
| CTC grade 1 (QTcF ≤ 470 msec) | No study drug adjustments |
| CTC grade 2 (470 < QTcF ≤ 500 msec) | No study drug adjustments Patient is to be referred to a cardiologist for evaluation and appropriate management. Patient can remain in the study (unless discontinuation is recommended by cardiologist) |
| CTC grade ≥ 3 (QTcF > 500 msec) | Dose is interrupted until a cardiologist consult obtained. If QTcF >500 is confirmed by cardiologist, the patient is to be discontinue |

See Section 6.3.3 for further guidance on QTcF adverse events

6.3.2 Follow-up for toxicities

Refer to [Table 6-2](#), [Table 6-3](#) and [Section 6.3.3](#).

6.3.3 Anticipated risks and safety concerns of the study drug

Appropriate eligibility criteria, specific dose modification and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced adverse events, i.e., hyperglycemia, QT prolongation and LFT abnormal are provided below. Refer to preclinical toxicity and or clinical data found in the [Investigator's Brochure].

6.3.3.1 Hyperglycemia

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

Monitoring of blood glucose

Close and frequent monitoring of blood glucose is needed during pasireotide treatment. The principal investigator is to educate the patient on the signs and symptoms of hyperglycemia. Patients must monitor their fasting blood glucose by fingerstick at home at least 3 times per week for the first month of pasireotide LAR treatment. If a patient does NOT have any fasting values above 100 mg/dL, monitoring can be decreased to at least 2 times per week for months 2 and 3 and 1 time every 2 weeks for 4 months through 6 months. If glucose values remain normal (lower than or equal to 100 mg/dL), monitoring is at the investigator's discretion after 6 months. If any values are observed above 100 mg/dL, the guidelines in [Figure 6-1](#) are to be followed. These guidelines are based on the current recommendations from the 2012 American Diabetes Association and European Association for the Study of Diabetes aiming at a glycemic treatment goal of FPG <130 mg/dL (<7.2 mmol/L). Appropriate actions such as initiation of anti-hyperglycemic therapy (and referral to diabetes specialist) are to be taken by the investigator as outlined on [Figure 6-1](#). If fasting blood glucose values dictate initiation of anti-hyperglycemic treatment (i.e., confirmed >130 mg/dL by self-monitoring), a fasting plasma glucose sample using the local laboratory is to be collected prior to initiation of anti-hyperglycemic treatment. If a patient has a dose increase, monitoring for hyperglycemia should follow the recommendations for the first month of treatment and continue as presented above for subsequent months.

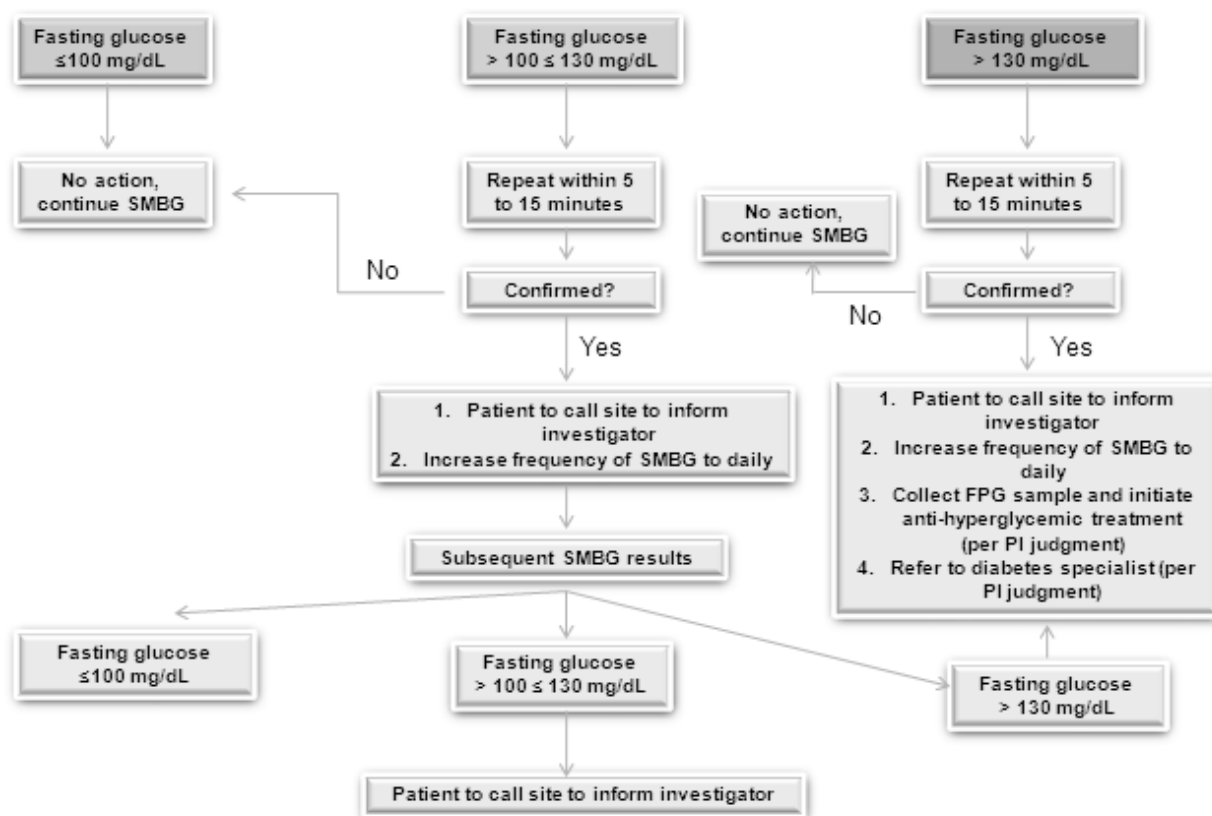
It is recommended that the patients be encouraged to keep a diary for their blood glucose for appropriate management throughout the study and present the collected data to their physician/diabetes specialist for evaluation. This data will not be collected by the sponsor.

In addition to self-monitoring, fasting plasma glucose and HbA1c will be collected at study visits per [Table 7-1](#) and [Table 7-2](#). Intervention for hyperglycemia is to be implemented in any patient meeting any of the following criteria: FPG > 130 mg/dL or HbA1c ≥ 6.5 %.

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

As outlined in [Table 6-2](#), patients with grade 3 hyperglycemia (FPG value >250 mg/dL; >13.9 mmol/L) at any point in the study should have the dose of pasireotide decreased. Patients who in spite of appropriate therapeutic interventions and despite dose reduction of study drug develop uncontrolled diabetes mellitus and/or consistently high blood glucose values: FPG ≥ 240 mg/dL (13.3 mmol/L) or HbA1c value ≥ 10 % will require study treatment discontinuation as outlined in [Section 7.1.3.1](#).

Figure 6-1 Fasting self-monitoring blood glucose guidelines



6.3.3.2 QT-related cardiology consultation / Holter monitoring

All patients will be asked to return on Day 22 for an ECG recording and PK sampling.

If at any visit a QTcF > 500 msec is observed, triplicate ECGs, each 2-3 minutes apart, need to be taken approximately 1 hour after the initial ECG. The mean QTcF from the triplicate ECGs will be determined. If the mean QTcF is > 500 msec, the patient has to postpone study treatment until a cardiologist has re-evaluated the ECG (this can be done by the central cardiologist). The re-evaluation needs to be done as soon as practical but within 7 days of the

initial abnormal ECG. If the cardiologist confirms a mean QTcF > 500 msec, the patient must be discontinued from the study. Otherwise and if the cardiologist confirms that at least one ECG shows a QTcF > 470msec, the cardiac assessments described for a confirmed QTcF > 470 msec needs to be followed.

If at Day 22 a QTcF / mean QTcF > 470 msec but \leq 500 msec is observed for the first time for a patient at a given dose level, the following steps need to be taken (please also refer to [Figure 6-2](#)):

A cardiology consultation must be sought as soon as practical but within 7 days of the initial abnormal ECG and prior to the next pasireotide LAR injection. The cardiologist must re-evaluate the ECG:

- If a QTcF > 470 msec is NOT confirmed, no further action needs to be taken.
- If a QTcF > 470 msec is confirmed, a cardiologist must perform a thorough examination (such as reviewing baseline ECG, concurrent medications and performing a cardiovascular examination, including at least a cardiac auscultation) to assess the patient for cardiovascular risk factors.
- If based upon the assessment by the cardiologist, the investigator considers that there is an acute cardiovascular safety risk and that the patient should not continue with study medication, the patient needs to be discontinued immediately (discontinuation criteria to be followed as described in [Section 7.1.3](#)).
 - If following the examination by the cardiologist, the investigator considers that there is no acute cardiovascular safety risk and that the patient could continue to receive study medication, a 24hr Holter ECG must be recorded at the next pasireotide LAR injection. The Holter-ECG must be started 30 min prior to an injection of study medication and a pre-dose PK sample will be taken.

If at any visit at trough level (28 days after the previous dose) a QTcF/mean QTcF > 470 msec but \leq 500msec is observed for the first time for a patient at a given dose level, the following steps need to be taken (please also refer to [Figure 6-2](#)):

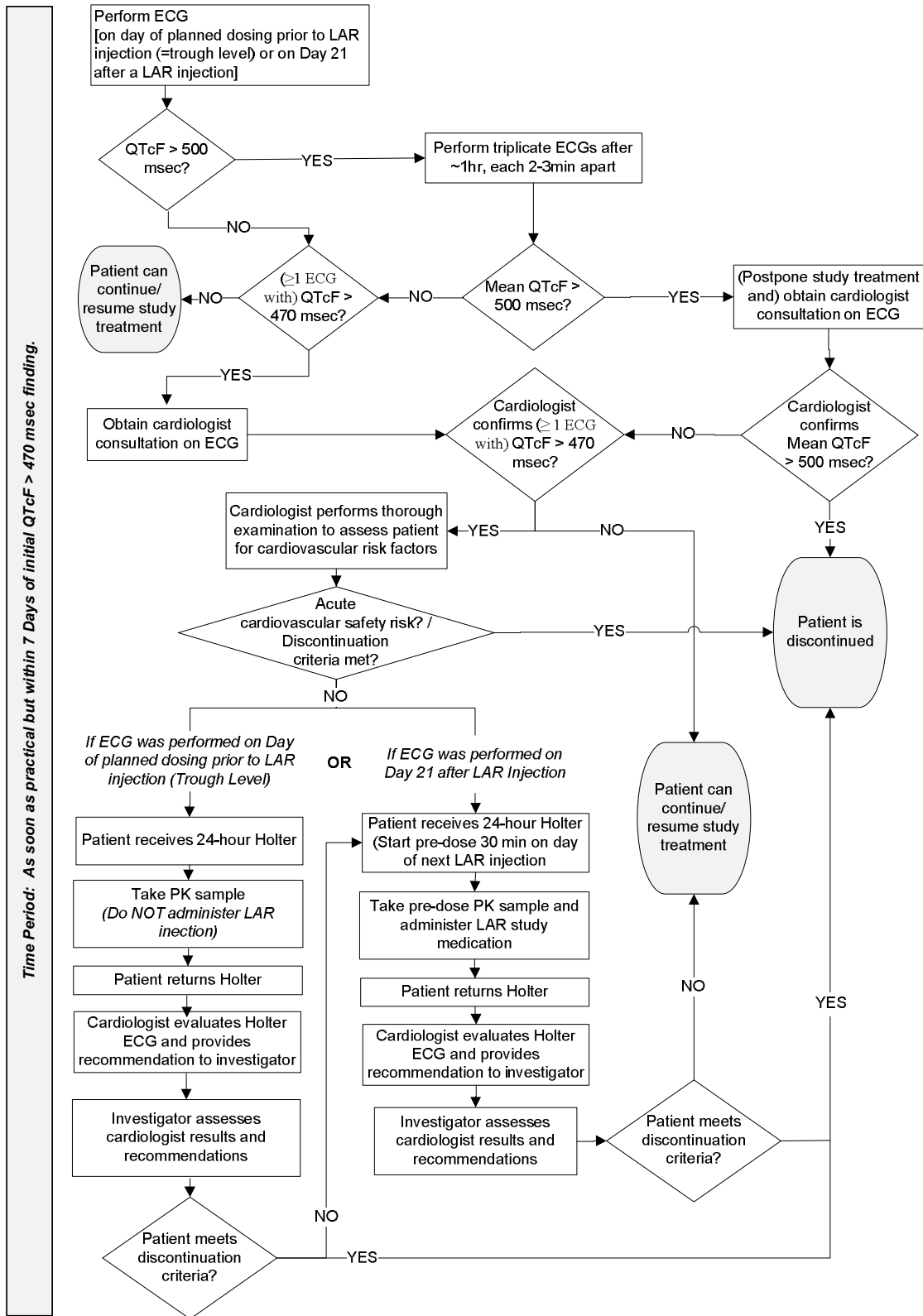
A cardiology consultation must be sought as soon as practical but within 7 days of the initial abnormal ECG and prior to the next pasireotide LAR injection. The cardiologist must re-evaluate the ECG.

- If a QTcF > 470msec is NOT confirmed, no further action needs to be taken.
- If a QTcF > 470msec is confirmed, a cardiologist must perform a thorough examination (such as reviewing baseline ECG, concurrent medications and performing a cardiovascular examination, including at least a cardiac auscultation) to assess the patient for cardiovascular risk factors.
- If based upon the assessment by the cardiologist, the investigator considers that there is an acute cardiovascular safety risk and that the patient should not continue with study medication, the patient needs to be discontinued immediately (discontinuation criteria to be followed).

- If following the examination by the cardiologist, the investigator considers that there is not an acute cardiovascular safety risk and that the patient could continue to receive study medication, a 24hr Holter ECG must be recorded and evaluated prior to the next injection of pasireotide LAR and a trough PK sample will be taken. The pasireotide LAR injection must be postponed with a maximal permissible delay of 7 days until the Holter-ECG results are available. If the outcome of the cardiac evaluation is that the patient may receive a further dose of pasireotide LAR, then a second 24hr Holter-ECG must be done on the day of the injection and a pre-dose PK sample must be taken. This Holter ECG should be started 30min prior to the injection.

The results of the ECGs, cardiac examination, Holter-ECGs and the recommendation by the cardiologist must be evaluated by the investigator to determine whether the patient should continue in the study or not (discontinuation criteria to be followed as described in [Section 7.1.3](#)).

Figure 6-2 QT prolongation monitoring flow chart



6.3.3.3 Hepatic safety management

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

- ALT or AST > 3 x ULN and Total Bilirubin \geq 2 x ULN
- ALT or AST > 5 x ULN and \leq 8 x ULN
- ALT or AST > 8 x ULN

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

- Perform liver-directed medical history and physical examination (i.e. assess occupational hazards, concomitant medications including OTC meds, inter-current illness, etc)
- Liver chemistry tests: ALT, AST, total bilirubin (fractionated to direct/indirect 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)
- Collect PK sample and record the dose level and the dosing time for the last dose the patient has taken prior to PK sampling

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

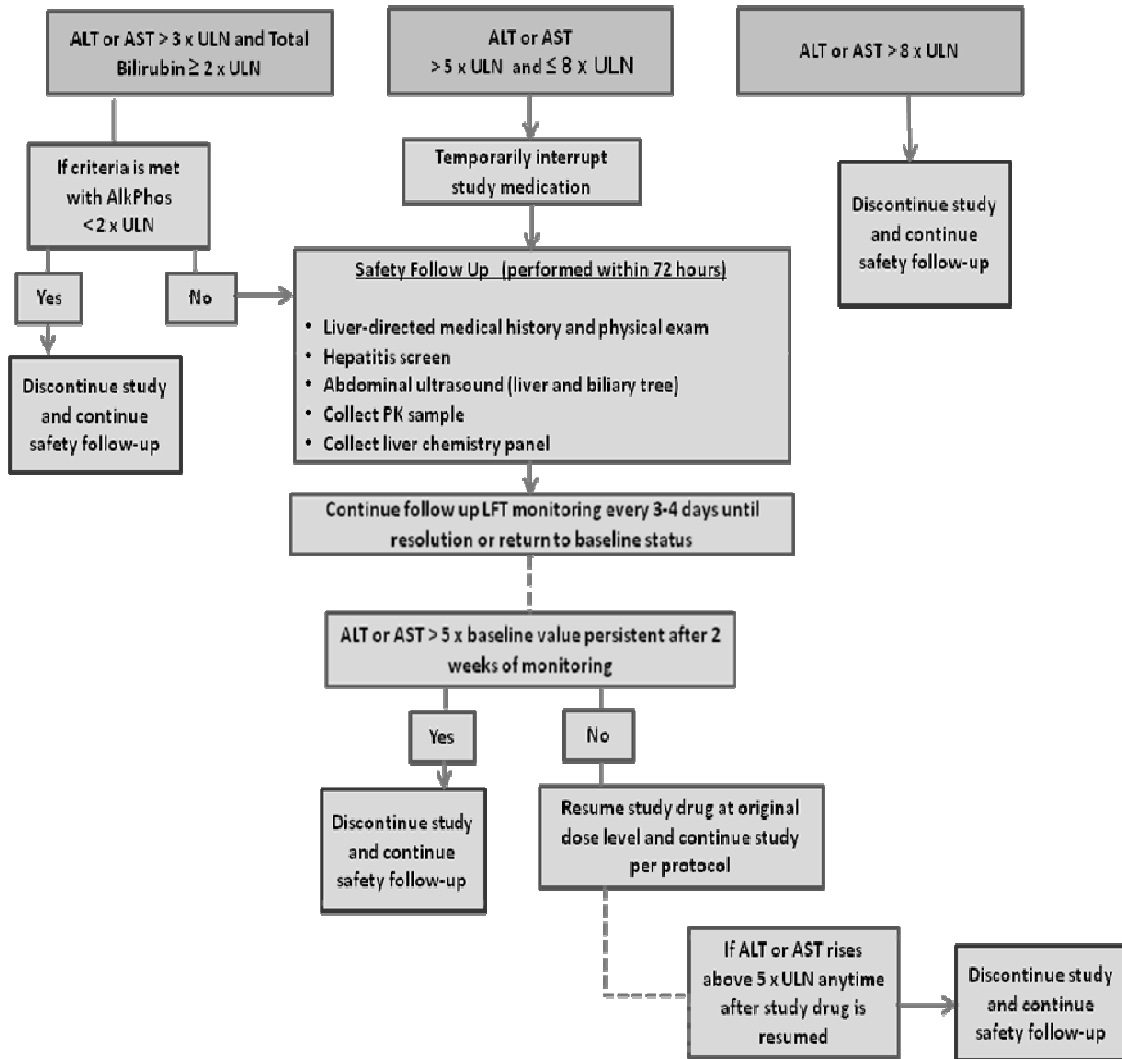
Patients or subjects may need to be discontinued if the abnormal liver function criteria are met upon LFT retesting (See criteria for premature withdrawal criteria [Section 7.1.3.1](#)). Progress reports of the event should be maintained until resolution or stabilization (i.e. no further elevation after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

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

- Study medication should be temporarily interrupted and liver chemistry tests monitored every **3-4 days** until resolution or return to baseline.
- If resolution or return to baseline does not occur after 2 weeks, the patient should be discontinued.
- If ALT or AST (or both if ALT and AST were elevated) 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 6-3 LFT management algorithm



6.4 Concomitant medications

6.4.1 Permitted concomitant therapy

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. As well as any changes in the dose of any medication the patient was taking prior to or during the study. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Concomitant Medications/Significant Non-Drug Therapies CRF. Note: Concomitant medications information will not be collected for the patients who continue the study treatment beyond 2 years (See Table 7-2). Diabetic patients must continue their treatment for diabetes throughout the study as indicated. If oral contraception is used, the patient must have been practicing this method of birth control for at least two months prior to enrollment and must agree to continue the oral contraceptive throughout the course of the study and for three months after the last dose of study drug.

6.4.2 Permitted concomitant therapy requiring caution and/or action

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

6.4.3 Prohibited concomitant therapy

For patients with medication naïve acromegaly or pituitary gigantism the single dose of short acting octreotide or short-acting dopamine agonists should not be administered within 3 days prior to Visit2 (baseline). In case of a single dose of short-acting octreotide, the dose should not be used to predict the response to the octreotide treatment.

The use of the following treatments is prohibited after start of study.

- Other investigational drug or therapy.
- Medication known to affect GH or IGF-1 concentration should not be taken during this study.

The use of concomitant medications with a known risk for QT prolongation is prohibited and requires the discontinuation of the patient from the study prior to starting the respective QT prolonging medication. Please refer to [Appendix 2](#) for guidance regarding medications which pose a known risk for QT prolongation.

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient numbering

Each patient is identified in the study by a Patient Number (Patient No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Patient No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each Patient is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Patient No. available to the investigator.

Only the assigned patient number should be entered in the field labeled “Patient number on the EDC data entry screen (e.g. enter ‘1’, ‘2’, etc.). Once assigned, the patient number must not be reused for any other patient and the patient number for that individual must not be changed, even if the patient is re-screened.

6.5.2 Treatment assignment or randomization

6.5.2.1 Randomization number

If the patient is deemed eligible for the study and will commence dosing, a randomization number will be assigned. Once assigned to a subject, a randomization number will not be reused.

Patients who have prior medications will be assigned randomization numbers [REDACTED] and patients who don't have prior medications will be assigned randomization numbers [REDACTED]

Table 6-4 Treatment assignment numbering

| | With prior medication | Without prior medication |
|-----------------------|-----------------------|--------------------------|
| Randomization numbers | [REDACTED] | [REDACTED] |

Patients will be assigned to one of the 3 treatment arms ([Section 4.1](#) and [Section 6.1](#)) in a ratio of 1:1:1.

Randomization will be stratified by prior medications (i.e. somatostatine analogue and dopamine agonist) (yes or no).

Randomization will be performed using the following procedure to ensure that treatment assignment is unbiased. Random permuted blocks scheme will be used for this study.

A randomization list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of treatment groups to randomization numbers in the specified ratio. The randomization list will be reviewed by a Biostatistics Quality Assurance Group and locked by them after approval.

Prior to dosing, all patients who fulfill all inclusion/exclusion criteria will be assigned the lowest available number on the randomization list.



6.5.3 Treatment blinding

This is an open-label study. However, in order to minimize the potential impact of treatment knowledge, treatment allocation, dose information and PK data will not be accessed by sponsor except data manager and CRA until it will be locked for the primary analysis. The investigators and patients have full knowledge of the treatment allocation.

6.6 Study drug preparation and dispensation

Novartis supplies pasireotide LAR to the investigational sites as 20 mg and 40mg vials. All dosages given to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

Instructions for Use can be found in [Appendix 1](#).

6.6.1 Study drug packaging and labeling

Pasireotide LAR will be provided as powder for suspension in vials and solution for suspension (“vehicle”) will be provided in ampoules. Medication labels will be in the local language and comply with the legal requirements of Japan. They will include storage conditions for the drug (For details, see study drug handling procedure which is provided by Novartis)

6.6.2 Drug supply and storage

Study treatments must be received by a 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 LAR should be stored according to the instructions specified on the study drug handling procedure.

For any further information on the formulation, storage and handling of SOM230, please consult the investigators brochure.

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

Study drug compliance will be assessed by the Dosage Administration Record. All information is to be noted in the Dosage Administration Record.

6.6.3.2 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.

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

6.6.3.3 Handling of other study treatment

Not applicable.

6.6.4 Disposal and destruction

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

7 Visit schedule and assessments

7.1 Study flow and visit schedule

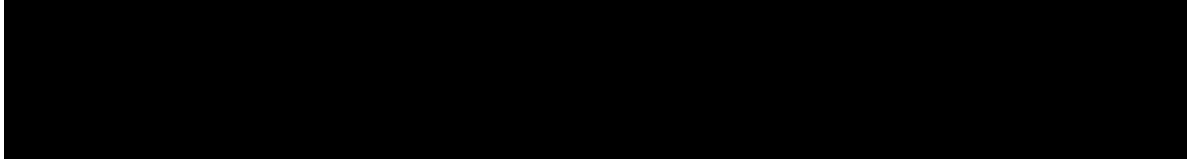
[Table 7-1](#) and [Table 7-2](#) list all of the assessments and indicate with an “X”, the visits when they are performed. All data obtained from these assessments must be supported in the patient’s source documentation. The table indicates which assessments produce data to be entered into the database (D) or remain in source documents only (S) (“Category” column).

The blood sampling schedule at each visit for PK and GH are shown in [Table 7-3](#). Patients are to fast overnight for at least 8 hours prior to all blood samples being taken.

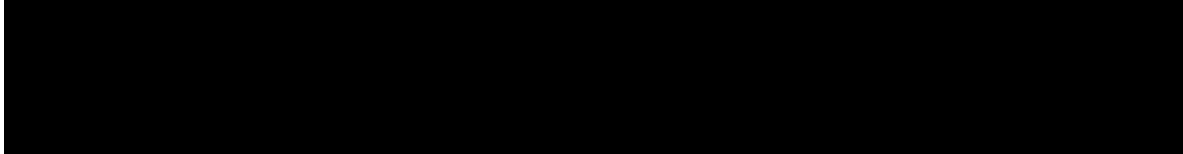
No CRF will be used as a source document.

Table 7-1 Visit evaluation schedule (core phase)

| | Category | Reference | Screening | Baseline | | | | | | | | | | | | | | | | End of study treatment Core phase ^D | Study completion |
|---|----------|------------|-----------|----------|---|----|------|----|----|------|----|-----|------|----|----------|-----|----------|-----|----------|--|---------------------------------|
| Visit number | | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13,14 | 15 | 16,17 | 18 | 19,20 | 777 | 779 |
| Study day | | | -28 to -1 | 1 | 2 | 15 | 22 | 29 | 43 | 50 | 57 | 71 | 78 | 85 | 113, 141 | 169 | 197, 225 | 253 | 281, 309 | 337 | 56 days following the last dose |
| Month (1 month = 28 days) | | | | 0 | | | 0.75 | 1 | | 1.75 | 2 | 2.5 | 2.75 | 3 | 4,5 | 6 | 7,8 | 9 | 10,11 | 12 | 14 |
| pasireotide LAR Injection ^A | D | 6.1 | | 1 | | | | 2 | | | 3 | | | 4 | 5,6 | 7 | 8,9 | 10 | 11,12 | | |
| Informed Consent | D | 11.3 | X | | | | | | | | | | | | | | | | | | |
| Inclusion/Exclusion criteria | S/D | 5.2, 5.3 | X | X | | | | | | | | | | | | | | | | | |
| Relevant Medical history | D | 7.1.1.3 | X | | | | | | | | | | | | | | | | | | |
| History of acromegaly or pituitary gigantism | D | 7.1.1.3 | X | | | | | | | | | | | | | | | | | | |
| Prior therapy for acromegaly or pituitary gigantism | D | 7.1.1.3 | X | | | | | | | | | | | | | | | | | | |
| Archival Tumour Sample | D | 7.2.4.1 | | X | | | | | | | | | | | | | | | | | |
| Demography | D | 7.1.1.3 | X | | | | | | | | | | | | | | | | | | |
| Physical Examination | S | 7.2.2.1 | X | X | | | X | X | | | X | | | X | X | X | X | X | X | X | X |
| Vital signs | D | 7.2.2.2 | X | X | | | X | X | | | X | | | X | X | X | X | X | X | X | X |
| Height | D | 7.2.2.3 | X | | | | | | | | | | | | | | | | | | |
| Weight | D | 7.2.2.3 | X | X | | | X | X | | | X | | | X | X | X | X | X | X | X | X |
| MRI | D | 7.2.1.3 | X | | | | | | | | | | | | | X | | | | X | |
| ECG | D | 7.2.2.5.1 | X | X | | | X | X | | | X | | X | X | X | X | X | X | X | X | X |
| Gallbladder ultrasound | D | 7.2.2.4.10 | X | | | | | | | | | | X | | X | | | X | | X | |
| Hematology | D | 7.2.2.4.1 | X | X | | | X | X | | | X | | | X | X | X | X | X | X | X | X |



| | Category | Reference | Screening | Baseline | | | | | | | | | | | | | | | | End of study treatment Core phase ^D | Study completion | |
|---|---------------------------------------|---------------------------|--------------------------|----------|----------------|----|------|----|----|------|----|-----|----------------|----------------|----------|----------------|----------|-----|----------|--|---------------------------------|---|
| Visit number | | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13,14 | 15 | 16,17 | 18 | 19,20 | 777 | 779 | |
| Study day | | | -28 to -1 | 1 | 2 | 15 | 22 | 29 | 43 | 50 | 57 | 71 | 78 | 85 | 113, 141 | 169 | 197, 225 | 253 | 281, 309 | 337 | 56 days following the last dose | |
| Month (1 month = 28 days) | | | | 0 | | | 0.75 | 1 | | 1.75 | 2 | 2.5 | 2.75 | 3 | 4,5 | 6 | 7,8 | 9 | 10,11 | 12 | 14 | |
| Coagulation Parameters (PT and APTT) | D | 7.2.2.4.2 | X | X | | | X | X | | X | X | | | X | X | X | X | X | X | X | X | X |
| HbA1c | D | 7.2.2.4.3 | X | X | | | | | | | | | | X | | X | | X | | X | X | X |
| Biochemistry (Including LFTs) | D | 7.2.2.4.3 | X | X | | | X | X | | | X | | | X | X | X | X | X | X | X | X | X |
| Fasting blood glucose | D | 7.2.2.4.3 | X | X | | | X | X | | | X | | | X | X | X | X | X | X | X | X | X |
| Fasting serum cortisol | D | 7.2.2.4.5 | | X | | | | | | | | | | X | | X | | X | | X | X | X |
| Plasma ACTH | D | 7.2.2.4.6 | | X | | | | | | | | | | X | | X | | X | | X | X | X |
| Urinalysis | D | 7.2.2.4.8 | X | X | | | | X | | | X | | | X | X | X | X | X | X | X | X | X |
| Symptoms of Acromegaly or pituitary gigantism | D | 7.2.1.4. | | X | | | | X | | | X | | | X | X | X | X | X | X | X | X | |
| Pregnancy test | D | 7.2.2.4.9 | X | X | | | | X | | | X | | | X | X | X | X | X | X | X | X | X |
| PK Blood collection | D | 7.2.3. | | X | | | X | X | | | X | X | X | X | X | X | X | X | X | X | X | |
| Efficacy assessments | GH profile | D | 7.2.1.1. | X | X | | | | | | | | X | X | | X | | X | | X | | |
| | PRL | D | 7.2.1.5. | X | X | | | | | | | | X | | | X | | X | | X | | |
| | IGF-1 | D | 7.2.1.2. | X | X | | | | | | | | X | X | | X | | X | | X | | |
| | GH suppression post OGTT ^B | D | | X | | | | | | | | | | | | | | | | | | |
| PD assessment | GH | D | 7.2.3 | | X | | X | X | | | X | X | X | X | X | X | | | | | | |
| | IGF-1 | D | 7.2.3 | | X ^C | | X | X | | | X | X | X ^C | X ^C | X | X ^C | | | | | | |



| | Category | Reference | Screening | Baseline | | | | | | | | | | | | | | | End of study treatment Core phase ^D | Study completion | |
|---|----------|---------------------------|------------------|----------|----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------------|------------|-----------------|------------|--|------------------|--|
| Visit number | | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13,14 | 15 | 16,17 | 18 | 19,20 | 777 | 779 |
| Study day | | | -28 to -1 | 1 | 2 | 15 | 22 | 29 | 43 | 50 | 57 | 71 | 78 | 85 | 113, 141 | 169 | 197, 225 | 253 | 281, 309 | 337 | 56 days following the last dose |
| Month (1 month = 28 days) | | | | 0 | | | 0.75 | 1 | | 1.75 | 2 | 2.5 | 2.75 | 3 | 4,5 | 6 | 7,8 | 9 | 10,11 | 12 | 14 |
| Free T4, TSH | D | 7.2.2.4.7 | X | X | | | | | | | | | | X | | X | | X | | X | X |
| Liver function test | D | 7.2.2.4.4 | | | | | | | | X | | | | | | | | | | | |
| HBsAg and AntiHCV | D | 7.2.2.4.4 | X | | | | | | | | | | | | | | | | | | |
| Study completion data | D | 7.1.3 | | | | | | | | | | | | | | | | | | X | X |
| Adverse events | D | 8.1, 8.3. | CONTINUOUS | | | | | | | | | | | | | | | | | | |
| Concomitant med | D | 6.4. | CONTINUOUS | | | | | | | | | | | | | | | | | | |
| Comments | D | | CONTINUOUS | | | | | | | | | | | | | | | | | | |
| <p>A. pasireotide LAR injection and study visits every 28 days +/- 2 days.</p> <p>B Patients' GH nadir within 2 hours after an oral glucose load with 75 g of glucose (OGTT) will be measured. The scheduled time points are at t0, oral glucose, t30, t60, t90, t120 (except for diabetic patients).</p> <p>C Blood sampling of IGF-1 for PD assessment combines with efficacy assessment.</p> <p>D For patients accepting to continue in the extension phase, at 12 months, a 13th injection of the same study treatment received in the core phase will be administered. Patients continuing the study treatment with pasireotide LAR in the extension phase will have the option of receiving pasireotide therapy as long as they do not fulfill any of the study discontinuation criteria or until pasireotide LAR is commercially available or until the pasireotide LAR development program is discontinued (whichever comes first).</p> <p>Visit 21 and Visit 777 are on the same day for patients willing to continue in the extension phase.</p> | | | | | | | | | | | | | | | | | | | | | |

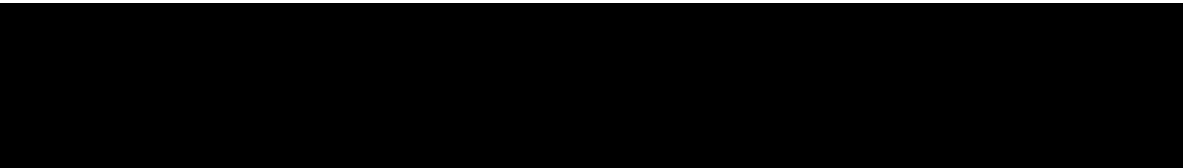
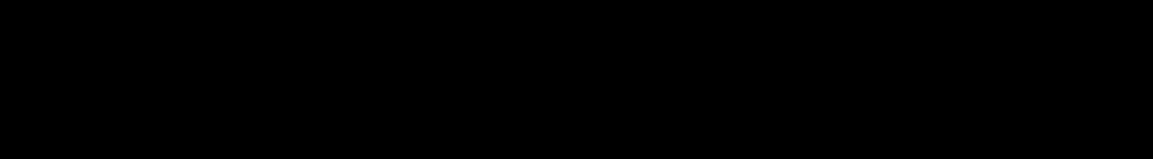


Table 7-2 Extension Visit evaluation schedule

| | Category | Reference | | | | | | | | | | | | | | | | End of study treatment for Ext | Study completion |
|--|----------|------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-------------------------|-----|---------------------------------|------------------|
| Visit number | | | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 and following visits | 778 | 779 | |
| Study day | | | 337 | 365 | 393 | 421 | 449 | 477 | 505 | 533 | 561 | 589 | 617 | 645 | 673 | 701, 729, 757, 813... | | 56 days following the last dose | |
| Month (1 month = 28 days) | | | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25- | | | |
| pasireotide LAR Injection ^A | D | 6.1 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26- | | | |
| Physical Examination | S | 7.2.2.1 | | X | X | X | X | X | X | X | X | X | X | X | X | | X | X | |
| Vital signs | D | 7.2.2.2 | | X | X | X | X | X | X | X | X | X | X | X | X | | X | X | |
| Weight | D | 7.2.2.3 | | X | X | X | X | X | X | X | X | X | X | X | X | | X | X | |
| ECG | D | 7.2.2.5.1 | | | | X | | | X | | | X | | | X | | X | X | |
| Gallbladder ultrasound | D | 7.2.2.4.10 | | | | X | | | X | | | X | | | X | | X | | |
| Hematology | D | 7.2.2.4.1 | | | | X | | | X | | | X | | | X | | X | X | |
| Coagulation Parameters (PT and APTT) | D | 7.2.2.4.2 | | | | X | | | X | | | X | | | X | | X | X | |
| HbA1c | D | 7.2.2.4.3 | | | | X | | | X | | | X | | | X | | X | X | |
| Biochemistry | D | 7.2.2.4.3 | | | | X | | | X | | | X | | | X | | X | X | |
| Fasting blood glucose | D | 7.2.2.4.3 | | X | X | X | X | X | X | X | X | X | X | X | X | | X | X | |
| Fasting serum cortisol | D | 7.2.2.4.5 | | | | X | | | X | | | X | | | X | | X | X | |
| Plasma ACTH | D | 7.2.2.4.6 | | | | X | | | X | | | X | | | X | | X | X | |
| Urinalysis | D | 7.2.2.4.8 | | | | X | | | X | | | X | | | X | | X | X | |
| Pregnancy test | D/S | 7.2.2.4.9 | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |



| | Category | Reference | | | | | | | | | | | | | | | End of study treatment for Ext | Study completion |
|--|------------|-----------|------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-------------------------|--------------------------------|---------------------------------|
| Visit number | | | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 and following visits | 778 | 779 |
| Study day | | | 337 | 365 | 393 | 421 | 449 | 477 | 505 | 533 | 561 | 589 | 617 | 645 | 673 | 701, 729, 757, 813... | | 56 days following the last dose |
| Month (1 month = 28 days) | | | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25- | | |
| Symptoms of Acromegaly or pituitary gigantism | D | 7.2.1.4 | | | | | | | X | | | | | | X | | X | |
| Efficacy assessments | GH profile | D | 7.2.1.1 | | | | | | X | | | | | | X | | X | |
| | PRL | D | 7.2.1.5 | | | | | | X | | | | | | X | | X | |
| | IGF-1 | D | 7.2.1.2 | | | | | | X | | | | | | X | | X | |
| Free T4, TSH | D | 7.2.2.4.7 | | | | X | | X | | | X | | | X | | X | X | |
| Liver function test | D | 7.2.2.4.4 | | | | X | | X | | | X | | | X | | X | X | |
| Study completion data | | | | | | | | | | | | | | | X | | X* | X* |
| Adverse events | D | 8.1, 8.3 | CONTINUOUS* | | | | | | | | | | | | | | | |
| Concomitant med | D | 6.4 | CONTINUOUS (up to 24 months) | | | | | | | | | | | | | | | |
| Comments | D | | CONTINUOUS* | | | | | | | | | | | | | | | |
| A. pasireotide LAR injection and study visits every 28 days +/- 2 days study treatment | | | | | | | | | | | | | | | | | | |

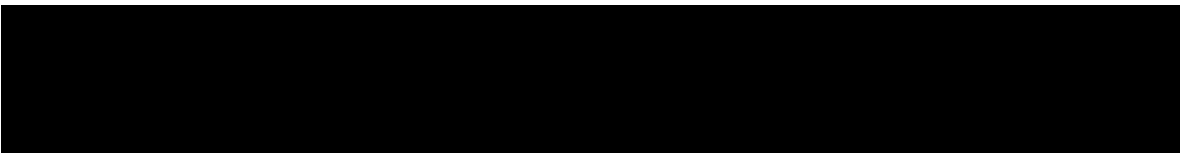


Table 7-3 Blood sampling schedule

| | -120 min | -90 min | -60 min | -30 min | 0 min | 120 min |
|-----------------------------------|---------------------|--------------------|--------------------|--------------------|------------------|--------------------|
| PK (Day 1,) | | | | | X | X |
| PK (except for Day 1) | | | | | X | |
| GH (Day 1, 85) | X | X | X | X | X | X |
| GH (Scr, Day 78, 169, 253, 337) | X | X | X | X | X | |
| GH (Day 22, 29, 57, 71, 113, 141) | | | | | X | |

7.1.1 Screening

Screening examination (Visit 1) is to include the procedures found in [Table 7-1](#) and should occur within 28 days prior to baseline. The informed consent must be signed prior to ANY screening procedure being performed. Patients that do not meet eligibility criteria are allowed to be rescreened. The rescreening should be documented in the source files. If the following procedures meet all inclusion and exclusion criteria at the original screening they do not have to be repeated for patients who rescreen within 60 days of baseline (Day 1): vital signs, MRI, and gallbladder ultrasound. Any of these assessments that are abnormal and all other assessments not listed here are to be repeated.

7.1.1.1 Eligibility screening

Manual process: Patient eligibility will be checked by the Registration center once all screening procedures are completed. The eligibility check form will be sent from the site to the Registration center either via fax or email for evaluation. Upon confirmation of eligibility, the Registration center will return the signed eligibility check form and inform assigned treatment arm to the site. Please refer and comply with detailed guidelines in the registration manual.

7.1.1.2 Information to be collected on screening failures

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the Screening Log Page. The Demography, Informed consent eCRF pages must be completed for Screen failure patients. No other data will be entered into the clinical database for patients who are screen failures. Please refer to [Section 8.2.2](#) for guidelines on SAE reporting requirements.

7.1.1.3 Patient demographics and other baseline characteristics

Standard demographic information and medical history will be collected. Acromegaly or pituitary gigantism history and diabetes history together with the medication/treatment used will also be collected. Other baseline assessments will be collected as per [Table 7-1](#).

7.1.2 Treatment period

The treatment period in the core phase of the study will be 12 months. Patients will have monthly visits with some visits more frequently (see [Table 7-1](#)). All visits should be performed on the indicated days. In cases where this is not possible, the following visit windows apply: +/- 2 days for visits 4-20 and 777, -2/+7 days for the 778, 779 and extension phase. Efforts should be made to have pasireotide LAR administration occurring as indicated in [Table 7-1](#) and [Table 7-2](#) at approximately the same time of day at each occurrence.

7.1.3 End of treatment visit including study completion and premature withdrawal

Patients who discontinue study treatment before visit 777 (if patient is in the core phase of the study) or visit 33 (if patient is in the extension phase of the study), should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the visit 777 / 778 will be performed ([Table 7-1](#) and [Table 7-2](#)). An End of Treatment eCRF page should be completed, giving the date and reason for stopping the study treatment.

At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations (visit 779) during 56 days following the last dose of study treatment.

Patients who discontinue study treatment should be considered withdrawn from the study after the final visit assessments are performed or when it is clear that the patient will not return for these assessments.

If a study withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the End of Treatment eCRF page. The investigator must inform the premature withdrawal to Novartis.

For criteria for premature withdrawal refer to [Section 7.1.3.1](#).

End of treatment visit and Study completion visit for patients treated for more than 2 years (after Visit 33)

If a patient discontinues after 2 years of treatment (after Visit 33), only the assessments with an asterisk in [Table 7-2](#) need to be performed on visit 778 and visit 779.

7.1.3.1 Criteria for premature patient withdrawal

Patients may voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time. Patients may be withdrawn from the study if any of the following occur:

- Adverse event(s) [including abnormal laboratory value(s) and abnormal test procedure result(s)]
- Protocol deviation (including but not limited to, new therapy for acromegaly, and discovery of patient ineligibility)
- Patient withdrew consent

- Lost to follow-up
- Administrative problems
- Death
- Disease progression
- Pregnancy
- Treatment duration completed as per protocol

The investigator must also inform the premature withdrawal to Novartis, if this occurs during the core period.

In addition to the general withdrawal criteria, the following **study specific criteria** will also require study treatment discontinuation:

- Patients experiencing unacceptable toxicity, as described in [Table 6-2](#), [Table 6-3](#).
- Patients unable to tolerate the lowest dose (20 mg) as per [Section 6.3](#).
- Patients with > 28 consecutive days of treatment interruption (either due to tolerability, investigator decision or patient compliance)
- Uncontrolled diabetes mellitus, consistently high glucose values FPG \geq 240 mg/dL (13.3 mmol/L) or HbA1c value \geq 10 % despite prior appropriate management and prior dose adjustment of the study drug,
- Patients experiencing adverse events in QTc:
 - a confirmed QTcF $>$ 470msec and discontinuation recommended by a cardiologist, or
 - Mean QTcF $>$ 500 msec measured by triplicate ECGs
 - Significant arrhythmia findings from Holter monitoring such as:
 1. Any ventricular or supra-ventricular tachyarrhythmia associated with symptoms of hemodynamic compromise
 2. Sustained ventricular tachycardia ($>$ 30 sec) irrespective of symptoms
 3. Recurrent non-sustained ventricular tachycardia (\geq 3 beats) during any 24-hour monitoring period
 4. Torsades de Pointes
 5. Cardiac arrest
 6. Pause $>$ 5 seconds
 7. Second or third degree AV block
 - New occurrence of clinically significant/symptomatic bradycardia, or
 - Increased risk of QT prolongation by use of QT prolonging medication, or
 - Hypokalemia ($<$ 3.5 mmol/L) or hypomagnesaemia ($<$ 0.7 mmol/L) confirmed by repeat testing that is either a new finding or accompanied by vomiting or diarrhea and not corrected by treatment.
- Patients experiencing the abnormal hepatic criteria below:
 - ALT or AST $>$ 3 x ULN and Total Bilirubin \geq 2 x ULN and ALP $<$ 2 x ULN
 - ALT or AST $>$ 5 x ULN and \leq 8 x ULN persistent for more than 2 weeks

- ALT or AST > 8 x ULN
- Lack of efficacy: during the core phase treatment period, patients with GH level > 2.5ug/L and/or IGF-1 > ULN (age and sex related) be discontinued from the study unless clinical benefit has been observed as per the investigator's judgment.

Patients who withdraw prematurely from the core phase cannot participate in the extension phase.

7.1.4 Follow up period

All patients must have safety evaluations for 56 days after the last dose of study treatment.

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. Patients that meet the requirements for follow up of abnormal LFTs should be followed up as detailed in [Section 6.3.3](#).

7.2 Assessment types

7.2.1 Efficacy assessments

7.2.1.1 GH (5-point mean GH level)

Patients' 5-point mean GH level will be assessed from a 2-hour profile after one hour at rest at the hospital before pasireotide LAR injection (for details please refer to [Table 7-1](#) and [Table 7-2](#)). The scheduled time points for blood sampling are t-120, t-90, t-60, t-30 and t-0 (pre-dose with respect to pasireotide LAR injection). All the GH 2 hour profiles should be taken at the same time (morning at around 8-10 am). The samples for GH will be analyzed by the central laboratory, [REDACTED]. Please refer to the [REDACTED] manual for processing details. This manual will be provided by [REDACTED].

7.2.1.2 IGF-1

Patient's total IGF-1 levels will be assessed with one pre-dose sample at the same visits as GH (for details please refer to [Table 7-1](#) and [Table 7-2](#)). T0 is defined as time point immediately pre-dose with respect to pasireotide LAR injection. The samples for IGF-1 will be analyzed by the central laboratory, [REDACTED]. Please refer to the [REDACTED] [REDACTED] for processing details. This manual will be provided by [REDACTED].

7.2.1.3 MRI

An MRI of the pituitary will be performed at visits indicated in [Table 7-1](#). MRI will not be performed during Extension phase. For *de-novo* patients an adenoma must be visible on screening MRI. The MRIs will be sent for evaluation by a central reader. To ensure consistency throughout all participating sites, the MRIs should be performed and processed following the guidelines from the central reader facility, which will be distributed to the sites before study start.



7.2.1.4 Symptoms of acromegaly or pituitary gigantism

The investigator will measure the patient's ring size using the gauge at visits indicated in [Table 7-1](#) and [Table 7-2](#). Ring size will be measured at the fourth digit of the non-dominant hand. In the case a patient has a fourth digit size exceeding the highest size; the fifth digit of that hand will be used for initial and follow-up investigation. The investigator will also ask the patient to score the following symptoms of acromegaly or pituitary gigantism: headache, fatigue, perspiration, paresthesia, osteoarthralgia according to a five-point score scale (0=absent, 1=mild, 2=moderate, 3=severe, 4=very severe)

7.2.1.5 Prolactin (PRL)

PRL levels will be assessed at visits indicated in [Table 7-1](#) and [Table 7-2](#). T0 is defined as time point immediately pre-dose with respect to pasireotide LAR injection. The samples for PRL will be analyzed by the central laboratory, [REDACTED]. Please refer to the [REDACTED] [REDACTED] for processing details.

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing hematology (including coagulation parameters), Biochemistry (including fasting blood glucose, glycosylated hemoglobin, LFTs), fasting serum cortisol, plasma ACTH, liver and thyroid function tests, urinalysis, injection site reactions, physical examinations including vital signs, gallbladder ultrasound, ECGs and body weight as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to [Section 8](#).

7.2.2.1 Physical examination

A complete physical examination will be performed by the investigator at visits indicated in [Table 7-1](#) and [Table 7-2](#).

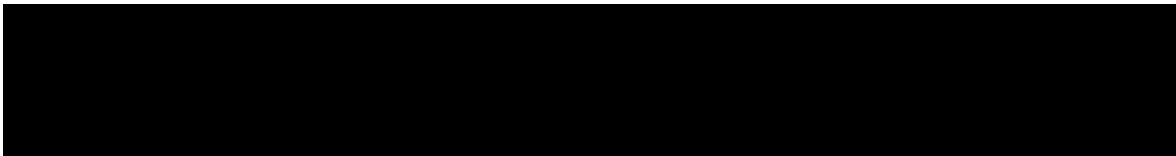
Information about the physical examination findings will be presented in the source documentation at the study site. Significant findings that were present prior to the signing of informed consent must be included in the Relevant Medical History/Current Medical Conditions page on the patient's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's eCRF.

7.2.2.2 Vital signs

Blood pressure, heart rate and body temperature will be assessed at visits indicated in [Table 7-1](#) and [Table 7-2](#) and recorded in the eCRF. Blood pressure and heart rate are to be taken after the patient has been in a supine position for 3 minutes.

7.2.2.3 Height and weight

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



7.2.2.4 Laboratory evaluations

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

Patients are to fast overnight for 8 hours prior to all blood samples being taken. Water is allowed during this time. The blood samples are to be taken before pasireotide LAR i.m. injection. Laboratory samples for hematology and blood chemistry will be analyzed locally.

Table 7-4 Clinical laboratory parameters collection plan

| Test Category | Test Name |
|----------------------------|--|
| Hematology (Local) | Hematocrit, Hemoglobin, Red blood cells, Platelets, White blood cells, WBC Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils) |
| Chemistry (Local) | Albumin, Alkaline phosphatase (ALP), Total Bilirubin, ALT (SGPT), AST (SGOT), GGT, Calcium, Chloride, Magnesium, Potassium, Sodium, Creatinine, Creatine kinase, Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN), Uric Acid, LDH, Inorganic phosphorus, Lipase and α -amylase, Fasting blood glucose, Glycosylated hemoglobin (HbA1c), If the total bilirubin concentration is increased above 2.0 times x ULN, total bilirubin should be differentiated into the direct and indirect reacting bilirubin. |
| Urinalysis (Local) | Dipstick (Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, pH, Protein, Specific Gravity) |
| Coagulation (Local) | Prothrombin time (PT), Activated partial thromboplastin time (APTT) |
| Thyroid (Local) | T4 [free], TSH |
| Hepatitis markers (Local) | Anti HAV IgM, HbsAg, HbcAb, anti HCV(if positive, PCR viral load should be assessed), Anti HEV, ANA antibodies, Anti smooth muscle anti-bodies, CMV and EBV |
| Additional tests (Central) | GH (Growth Hormone), Insulin-like growth factor 1 (IGF-1), Prolactin, Cortisol, ACTH |

7.2.2.4.1 Hematology

Hematology will be assessed locally at the site at visits indicated in [Table 7-1](#) and [Table 7-2](#). Hematology will include: WBC count with differential, hemoglobin, hematocrit, RBC count and platelet count.

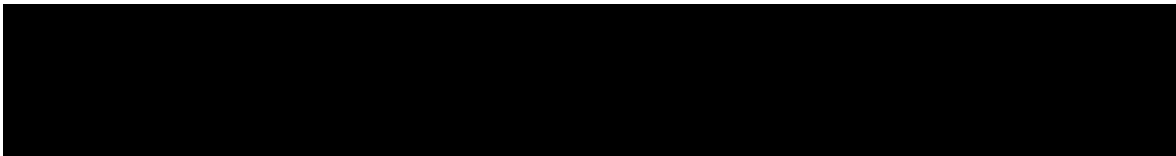
7.2.2.4.2 Coagulation

PT and activated partial thromboplastin time (APTT) will be assessed locally at the site at visits indicated in [Table 7-1](#) and [Table 7-2](#).

7.2.2.4.3 Biochemistry

Fasting biochemistry (including fasting blood glucose) will be assessed locally at the site at visits indicated in [Table 7-1](#) and [Table 7-2](#).

Albumin, Alkaline phosphatase (ALP), Total Bilirubin, ALT (SGPT), AST (SGOT), GGT, Calcium, Chloride, Magnesium, Potassium, Sodium, Creatinine, Creatine kinase, Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN), Uric Acid, LDH, Inorganic phosphorus, Lipase and α -amylase, Fasting blood glucose, Glycosylated hemoglobin (HbA1c),



If the total bilirubin concentration is increased above 2.0 times x ULN, total bilirubin should be differentiated into the direct and indirect reacting bilirubin.

7.2.2.4.4 Liver function testing

Presence of HBsAg and AntiHCV are to be assessed during screening.

At Visit 8 (Day 50) a full chemistry panel is not required and only the following Liver chemistry tests (LFTs) will be measured: ALT, AST, total bilirubin, direct bilirubin, indirect bilirubin, Alb, ALP and GGT.

If at any visit abnormal liver function criteria as described in [Section 6.3.3](#) are met, the following should be performed immediately within 72 hours of awareness of the abnormality:

- Liver chemistry tests: ALT, AST, total bilirubin (fractionated to direct/indirect if total bilirubin is $> 2.0 \times$ 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 antibodies, CMV and EBV

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

7.2.2.4.5 Serum cortisol

One pre-dose sample for fasting serum cortisol will be taken early in the morning at visits indicated in [Table 7-1](#) and [Table 7-2](#) and assessed at the central laboratory.

It is strongly recommended to take the sample for fasting serum cortisol between 7 and 9 am as this is the peak time for the cortisol secretion.

7.2.2.4.6 ACTH

A pre-dose blood draw for plasma ACTH sampling will be taken at visits indicated in [Table 7-1](#) and [Table 7-2](#) and assessed at the central laboratory.

7.2.2.4.7 Thyroid function tests

Free T4 and TSH will be assessed at visits indicated in [Table 7-1](#) and [Table 7-2](#). These tests will be performed and assessed locally at the site.

7.2.2.4.8 Urinalysis

Specific gravity, pH, semi-quantitative “dipstick” evaluation of glucose, protein, bilirubin, ketones, leukocytes and blood will be assessed at visits indicated in [Table 7-1](#) and [Table 7-2](#).

7.2.2.4.9 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have a serum hCG- β pregnancy test at visits indicated in [Table 7-1](#) and [Table 7-2](#). Note: Up to Visit 33, serum pregnancy test will be done and after Visit 33, serum or urine pregnancy test will be done and this data remain in source documents only. A positive serum or urine pregnancy test requires immediate interruption of study treatment until the assessment is confirmed. If positive, the patient must be discontinued from the study.

7.2.2.4.10 Gallbladder ultrasound

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

7.2.2.5 Cardiac assessments

7.2.2.5.1 Electrocardiogram (ECG)

A 12-lead ECG and a rhythm strip will be performed in supine position at the sites at visits indicated in [Table 7-1](#) and [Table 7-2](#).

All ECGs should include all 12 standard leads and a Lead II rhythm strip of at least a 10-second duration. The ECGs will be performed on the machine(s) provided for the study by the central reader and are sent to the central reader for evaluation. To ensure consistency throughout all participating sites, the ECGs should be performed and processed following the guidelines from the central reading facility, which will be distributed to the sites.

A Holter ECG will be required in case of a confirmed QTcF > 470 msec ([Section 6.3.3](#)).

7.2.2.6 Tolerability

In addition to general safety data, information on dose reductions will be collected.

7.2.3 Pharmacokinetics

To assess the pharmacokinetic profile of pasireotide administered as LAR, blood samples will be collected at the predefined time points ([Table 7-5](#)) and plasma concentration of pasireotide will be measured. The time of blood collection will be recorded on the PK blood collection eCRF page.

Descriptive statistics and graphical depiction (mean and individual) for pasireotide plasma concentrations during the course of treatment will be performed.

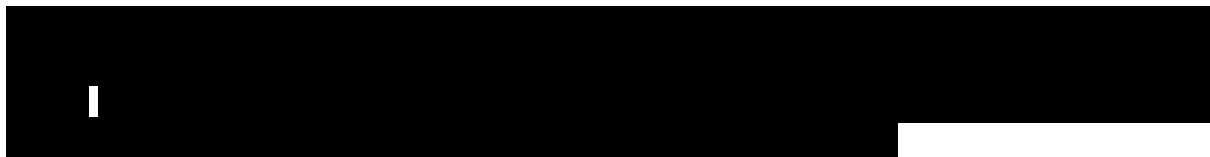


Table 7-5 Blood sampling for PK assessment

| Sample | Volume (mL) | Visit | Week | Day | PK Collection number | Sample number | Scheduled time (hr) |
|--------|-------------|-------|------|-----|----------------------|-------------------|-------------------------------|
| Blood | 2.5 | 2 | 0 | 1 | 1 | 1 | 0 (pre-dose) |
| Blood | 2.5 | 2 | 0 | 1 | 1 | 2 | 2 |
| Blood | 2.5 | 5 | 3 | 22 | 1 | 6 | 504 |
| Blood | 2.5 | 6 | 4 | 29 | 2 | 7 | 672/0 (pre-dose) ¹ |
| Blood | 2.5 | 9 | 8 | 57 | 3 | 9 | 672/0 (pre-dose) ¹ |
| Blood | 2.5 | 10 | 10 | 71 | 3 | 10 | 336 |
| Blood | 2.5 | 11 | 11 | 78 | 3 | 11 | 504 |
| Blood | 2.5 | 12 | 12 | 85 | 3, 4 | 12 | 672/0 (pre-dose) ¹ |
| Blood | 2.5 | 13 | 16 | 113 | 5 | 13 | 0 (pre-dose) |
| Blood | 2.5 | 14 | 20 | 141 | 6 | 14 | 0 (pre-dose) |
| Blood | 2.5 | 15 | 24 | 169 | 7 | 15 | 0 (pre-dose) |
| Blood | 2.5 | 16 | 28 | 197 | 8 | 16 | 0 (pre-dose) |
| Blood | 2.5 | 17 | 32 | 225 | 9 | 17 | 0 (pre-dose) |
| Blood | 2.5 | 18 | 36 | 253 | 10 | 18 | 0 (pre-dose) |
| Blood | 2.5 | 19 | 40 | 281 | 11 | 19 | 0 (pre-dose) |
| Blood | 2.5 | 20 | 44 | 309 | 12 | 20 | 0 (pre-dose) |
| Blood | 2.5 | 777 | 48 | 337 | 12 | 21 | 672 ² |
| Blood | 2.5 | NA | NA | NA | NA | 1001 ³ | Unscheduled |

1 : These samples are treated as samples for 672 hours post dose and pre-dose samples as well.
 2 : The sample must be obtained before pasireotide LAR administration if the subject is enrolled in the extension phase
 3 : Unscheduled blood samples must be uniquely and sequentially numbered from 1001, eq., 1001, 1002...

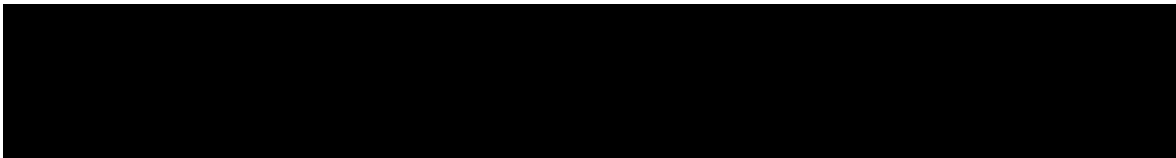
7.2.3.1 Pharmacokinetic blood sample collection and handling

All blood samples will be taken by either direct venipuncture or indwelling cannula inserted in a forearm vein. 2.5 mL of blood will be collected into an EDTA tube to yield 1mL of plasma for analysis of pasireotide plasma concentration. Immediately after blood is drawn into EDTA tubes, they should be inverted gently several times to ensure the mixing of tube contents. Prolonged exposure to the rubber stopper should be avoided. The tube should be placed upright in tube rack surrounded by ice until centrifugation. Within 20 minutes after blood collection, the sample should be centrifuged between 3 and 5°C for 10 minutes at approximately 1000 x g. Immediately after centrifugation, 1.0 mL plasma should be transferred to a polypropylene screw cap tube immersed in dry ice. The storage temperature for PK samples should be at or below -20°C.

PK samples will be taken in the case of a confirmed QTcF > 470msec (described in [Section 6.3.3.2](#)).

If at any visit abnormal liver function criteria as described in [Section 6.3.3](#) are met, the following should be performed within 72 hours of awareness of the abnormality:

- Collect PK sample and record the dose level and the dosing time for the last dose the patient has taken prior to PK sampling



The time of blood collection will be recorded on the PK blood collection eCRF page (e.g. the actual date/time of blood samples will recorded relative to the dose).

7.2.3.2 Analytical method

Pasireotide plasma concentrations will be measured using a validated radio-immunoassay (RIA) with a lower limit of quantification (LLOQ) of at least 0.15 ng/mL (150 pg/mL).

PK samples will be shipped to Atlanbio for bioanalysis.

[REDACTED]

7.2.5 Other assessments

No additional tests will be performed on patients entered into this study.

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).

[REDACTED]

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events eCRF. Conditions that were already present at the time of informed consent should be recorded in the Relevant Medical History/Current Medical Conditions eCRF. Adverse event monitoring should be continued for at least 56 days following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected in the End of Treatment or End of Study 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)
5. Whether medication or therapy taken (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](#)

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 eCRF. However the elevation of GH, IGF-1 and PRL values should not be reported as an adverse event.

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

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events eCRF. 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 (*optional*)

Adverse events of special interest include but may not be limited to AE's related to the following preferred terms: arrhythmogenic potential, bradycardia, coagulation, constipation, diabetes insipidus, diarrhoea, gall bladder and biliary, GI bleeding, GH deficiency, hyperglycemia, hypocalcemia, hypocortisolism, hypotension, hypothyroidism, injection site reaction, liver safety, low blood cells, nausea, pancreatitis, QT prolongation, and rhabdomyolysis.

8.1.3.1 Definitions and reporting

Groupings of adverse event of special interest will be considered and the number of patients with at least one event in each grouping will be reported. Such groups consist of AEs for which there is a specific interest in connection with SOM230 treatment (i.e. where SOM230 may influence a common mechanism of action responsible for triggering them) or adverse event that are very similar although not identical. The groups will be defined according to criteria described in MedDRA

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
- Protocol exempt SAEs: Add any additional SAEs specifically defined by the protocol and where there has been a clear agreement with regulators not to collect these SAEs in the safety database, provided the information is collected elsewhere. For example, this may include serious adverse events that are also a primary outcome measure, such as mortality, survival rate or number of flares of the condition being studied.

8.2.2 Reporting

To ensure patient safety, every SAE, **regardless of suspected causality**, occurring after the patient has provided informed consent and until at least 56 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after this 56 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; 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, and send the completed, signed form by fax within 24 hours to the oncology Novartis Drug Safety and Epidemiology (DS&E) department.

The telephone and telefax number of the contact persons in the local department of Drug Safety and Epidemiology (DS&E), specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. The follow up period for a newborn of a patient or a partner who becomes pregnant during the study and up to 3 months post last pasireotide LAR dose, is 3months.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology Department (DS&E). 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.

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.

8.4 Warnings and precautions

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

9 Data collection and management

9.1 Data confidentiality

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

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

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

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

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and 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. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the 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 eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

All central labs including pharmacokinetic (PK) and Biomarker (tissue) samples drawn during the course of the study will be collected from the investigator sites and analyzed by Novartis or a central lab contracted by Novartis. The site staff designated by the investigator will enter the information required by the protocol onto the PK and Biomarker sample collection eCRFs, respectively, as well as the designated CRO's requisition form. One copy of the requisition form will be forwarded to the central lab along with the corresponding samples with required information (including study number, patient ID, etc.) and one copy will be retained by the site.

ECG tracings and radiological scans will be transferred to a central reader.

9.4 Database management and quality control

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

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

Samples and/or data will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO) for the following: biomarkers, PK, central radiology and ECGs.

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

In this study, the results will be reported several times. The first report is planned when the last patient completes 3 months assessment. The result of the primary endpoint will be summarized. On emerging safety concerns observed during the early study period, the second report may be planned when the last patient completes 6 months assessment. The subsequent report is planned when the last available patient completes 12 months assessment. An additional report will be prepared after all patients end study treatment.

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned by randomization. According to the intent to treat principle, patients will be analyzed according to the study treatment they have been assigned to during the randomization procedure.

10.1.2 Safety Set

The Safety Set includes all patients who received at least one dose of study treatment. Patients will be analyzed according to the study treatment they actually received.

A precise definition of “actually received” will be added in the RAP.

10.1.3 Per-Protocol Set

The Per-Protocol Set (PPS) consists of a subset of the patients in the FAS without any major protocol deviation and who received at least one dose of study treatment.

Any protocol deviations leading to exclusion from the PPS will be detailed in the validation and planning (VAP) Module 3.

10.1.4 Dose-determining analysis set

Not applicable

10.1.5 Pharmacokinetic analysis set

The pharmacokinetic analysis set (PAS) consists of FAS who have evaluable pharmacokinetic concentration data.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data (e.g. age, sex) will be summarized descriptively by study treatment group for the FAS. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum and maximum will be presented.

10.3 Study treatments (study treatment, concomitant therapies, compliance)

The number of study drug administration will be summarized by dose levels and total-group for Safety set.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized by dose level study treatment and total-group for the Safety Set.

10.4 Primary objective

The primary objective is to assess the efficacy of pasireotide LAR on the reduction of mean GH levels to $< 2.5\mu\text{g/L}$ and the normalization of IGF-1 at 3 months of study treatment.

10.4.1 Variable

The primary variable is the total-group response rate defined as the proportion of patients with the reduction of mean GH levels to $< 2.5\mu\text{g/L}$ and the normalization of IGF-1 at 3 months of study treatment.

10.4.2 Statistical hypothesis, model, and method of analysis

The total-group response rate at 3 months of study treatment along with the corresponding Clopper-Pearson exact two-sided 90% confidence interval will be provided. The primary analysis will be performed on the FAS.

10.4.3 Handling of missing values/censoring/discontinuations

If the GH and/or IGF-1 samples are taken after 35 days from the date of any LAR injection, the values of GH and/or IGF-1 at the corresponding visit will be treated as missing. In addition, if a patient has less than 3 samples for the assessment of 5-point mean GH levels from the 2-hour profile, the mean GH levels will be considered as missing.

The patients with missing values of mean GH levels and/or IGF-1 at 3 months of study treatment or who discontinue prior to the assessment at 3 months of study treatment will be considered as non-responders.

10.4.4 Supportive analyses

The primary analysis will also be repeated on the PPS.

As subgroup analysis, the primary analysis will also be repeated by prior medication (i.e., somatostatine analogue and dopamine agonist) (yes or no) on the FAS if the number of patients in the subgroup is large enough.

The total-group response rate at 3 months of study treatment along with the corresponding Clopper-Pearson exact 95% confidence interval will be provided on the FAS and PPS.

10.5 Secondary objectives

All secondary efficacy endpoints will be based on the FAS. All secondary endpoints measured up to 3 months of study treatment will be summarized by dose level at randomization study treatment and total-group. All secondary endpoints measured after 3 months of study treatment will be summarized by total-group only.

10.5.1 Key secondary objective(s)

Table 10-1 shows the primary, key secondary and secondary variables for core phase by time point. Table 10-2 shows the secondary variables for extension phase by time point. For the detailed key secondary objectives and secondary objectives, please refer to Table 3-1.

For other key secondary objectives, please refer to Section 10.5.3 (safety and tolerability) and Section 10.5.4 (PK).

Table 10-1 Primary and secondary variables for core phase

| Variables | 3M | 6M | 9M | 12M |
|---|---------------------------------------|-----------------|-----------------|-----------------|
| Proportion of patients with the reduction of mean GH levels to < 2.5µg/L and the normalization of IGF-1 | P (total-group) KS (by dose level) | S (total-group) | S (total-group) | S (total-group) |
| Proportion of patients with the reduction of mean GH levels to < 2.5µg/L | KS (total-group and by dose group) | S (total-group) | S (total-group) | S (total-group) |
| Proportion of patients with the normalization of IGF-1 | KS (total-group and by dose group) | S (total-group) | S (total-group) | S (total-group) |
| Change of tumor volume from baseline | | S | | S |
| Change of mean GH level from baseline | S | | | |
| Symptoms of acromegaly | S | | | |
| Change of PRL level from baseline | S | | | |

P: primary endpoint, KS: key secondary endpoint, S: secondary endpoint

Table 10-2 Primary and secondary variables for core phase

| Variables | 15M | 18M | 21M | 24M |
|---|-----|-----|-----|-----|
| Proportion of patients with the reduction of mean GH levels to < 2.5µg/L and the normalization of IGF-1 | | S | | S |
| Proportion of patients with the reduction of mean GH levels to < 2.5µg/L | | S | | S |
| Proportion of patients with the normalization of IGF-1 | | S | | S |
| Change of mean GH level from baseline | S | | | |

S: secondary endpoint

The response rate at 3 months of study treatment along with the corresponding exact 95% confidence interval will be provided by dose level at randomization study treatment.

For patients with the reduction of mean GH levels to $< 2.5 \mu\text{g/L}$ and patients with the normalization of IGF-1 at 3 months of study treatment, total-group proportions of patients along with the corresponding Clopper-Pearson exact two-sided 95% confidence interval will be provided. The same analyses will be performed by dose level at randomization study treatment.

10.5.2 Other secondary efficacy objectives

10.5.2.1 Other secondary efficacy analyses for core phase

For patients with the reduction of mean GH levels to $< 2.5 \mu\text{g/L}$ and normalization of IGF-1, patients with the reduction of mean GH levels to $< 2.5 \mu\text{g/L}$ and patients with the normalization of IGF-1 at 6, 9 and 12 months of study treatment, total-group proportions along with the corresponding Clopper-Pearson exact two-sided 95% confidence interval will be provided.

Changes of tumor volume at 6 and 12 months of study treatment from baseline will be summarized.

Changes of mean GH level from baseline will be summarized.

Changes of ring size from baseline will be summarized. The shift tables from baseline to the most extreme post-baseline value will also be presented for acromegaly symptoms other than ring size (headache, fatigue, perspiration, paresthesias, and osteoarthralgia).

Changes of PRL level from baseline will be summarized.

10.5.2.2 Other secondary efficacy objectives for extension phase

For patients with the reduction of mean GH levels to $< 2.5 \mu\text{g/L}$ and normalization of IGF-1, patients with the reduction of mean GH levels to $< 2.5 \mu\text{g/L}$ and patients with the normalization of IGF-1 at 18 and 24 months of study treatment, total-group proportions along with the corresponding Clopper-Pearson exact two-sided 95% confidence interval will be provided.

Changes of mean GH level from baseline will be summarized.

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used. All listings and tables will be presented appropriately.

For each safety variables to be summarized by summary tables, followings will be provided:

1. Summary table by dose level for variables measured up to 3 months of study treatment
2. Summary table for overall patients for variables measured after 3 months of study treatment

For each safety variables to be summarized by shift tables, followings will be provided:

1. Shift table by dose level to compare baseline to the worst value(s) measured up to 3 months of study treatment
2. Shift table for overall patients to compare baseline to the worst value(s) of all post-baseline values

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

1. pre-study treatment period: from day of patient's informed consent to the day before first dose of study medication
2. on-study treatment period: from day of first dose of study medication to 56 days after last dose of study medication
3. post-study treatment period: starting at day 57 after last dose of study medication.

10.5.3.2 Adverse events (AEs)

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

The incidence of study treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class, preferred term, severity (based on CTCAE grades), type of adverse event and 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.

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

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

The incidence of study treatment-emergent adverse events (new or worsening from baseline) occurred in core phase and extension phase will be summarized separately by system organ class, preferred term, severity (based on CTCAE grades), type of adverse event and relation to study treatment.

10.5.3.3 Laboratory abnormalities

For laboratory tests covered by the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (see NCI 2006), the study's biometrics and statistical reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

In cases differentials count, the lower limits of normal ranges used in CTCAE definition have to be replaced by a clinical meaningful limit expressed in absolute counts.

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

The following summaries will be generated by dose level or total-group for hematology, biochemistry and urinary laboratory tests:

- frequency table for newly occurring on-study treatment grades 3 or 4
- shift tables using CTCAE grades to compare baseline to the worst on-study treatment value
- for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/low and high classification to compare baseline to the worst on-study treatment value
- listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

10.5.3.4 Other safety data

ECG

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

Vital signs

Definitions of notably abnormal results have to part of the MAP, CSP and/or RAP.

- shift table baseline to worst on-study treatment result
- listing of vital signs for all patients with at least one notably abnormal result

Gallbladder Ultrasound

Gallbladder data at each visit will be listed.

10.5.3.5 Tolerability

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

10.5.4 Pharmacokinetics

PAS will be used in all pharmacokinetic data analysis and summary statistics.

Pharmacokinetic variables

The following PK parameters (Table 10-3) will be determined using non-compartmental method.

Table 10-3 Pharmacokinetic parameters for LAR formulations

| i.m. LAR dose | |
|---------------------------|---|
| $C_{\text{trough day28}}$ | The trough level concentration on day 28 post each injection of LAR, expressed as $C_{\text{trough day28, 1st inj}}$, $C_{\text{trough day28, 2nd inj}}$, $C_{\text{trough day28, 3rd inj}}$ etc. |
| $C_{\text{max,3rd inj}}$ | The maximum concentration post the 3 rd injection of LAR |
| AR | The accumulation ratio calculated as a ratio of [$C_{\text{trough day28,3rd inj}} / C_{\text{trough day28,1st inj}}$] |

Descriptive statistics of pasireotide plasma concentrations will be provided by each time point and dose. Descriptive statistics of PK parameters will be provided by dose. Descriptive statistics will include arithmetic and geometric mean, median, SD, and CV, geometric CV, minimum and maximum. Zero concentrations will not be included in the geometric mean calculation. The concentration data and the PK parameters obtained after dose increase/reduction will be summarized separately.

The effect of patient demographics (e.g. age, body weight, BMI and gender) on PK will be explored, if applicable.

Statistical methods for pharmacokinetic analyses:

The relationship between the dose and the PK parameters ($C_{\text{troughday28,3rd inj}}$) will be explored by the following linear model on the log scale:

$$\ln(\text{PK parameters}) = \text{intercept} + \text{slope} * \ln(\text{Dose}) + \text{error}.$$

In this model, the dose-exposure relationship is mainly characterized by the slope parameter: a value lower/higher than 1 indicates an under/over proportional dose-exposure relationship. The point estimate and associated 90% CI for the slope parameter will be provided for each PK parameters. Point estimates and the corresponding 90% CIs for the PK ratios of 40 mg versus 20 mg and 60 mg versus 20 mg will be presented on the original scale.

10.5.4.1 Data handling principles

Plasma concentrations of pasireotide will be expressed in ng/mL. All concentrations below the limit of quantitation or missing data will be reported as such in the concentration data listings. Concentrations below the limit of quantitation will be treated as zero in summary statistics.

10.5.5 Biomarkers

10.5.5.1 Outline of the data analysis

Not applicable.

10.5.5.2 Data handling principles

Not applicable.

10.5.5.3 Data analysis principles

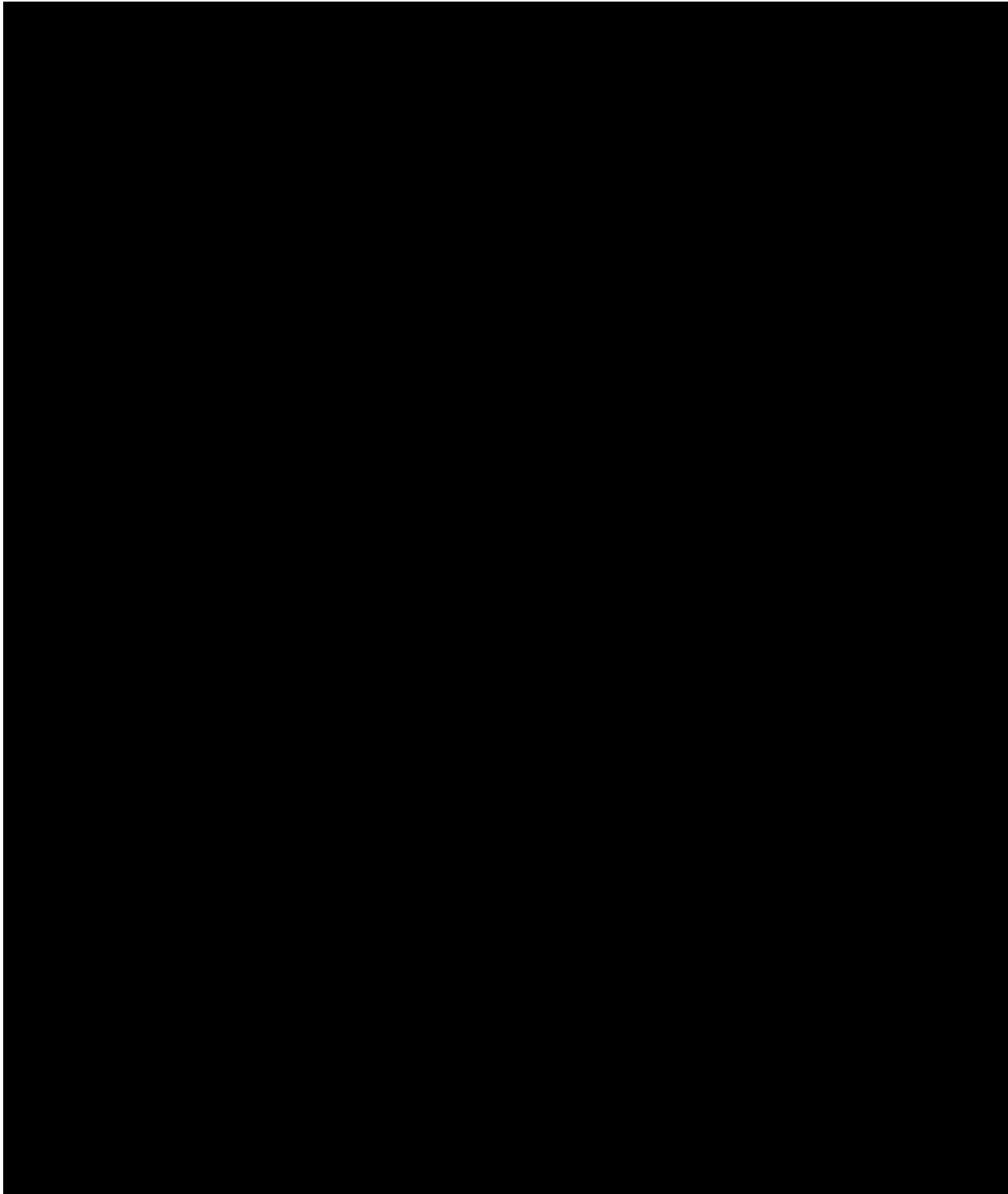
Not applicable.

10.5.6 Resource utilization

Not applicable.

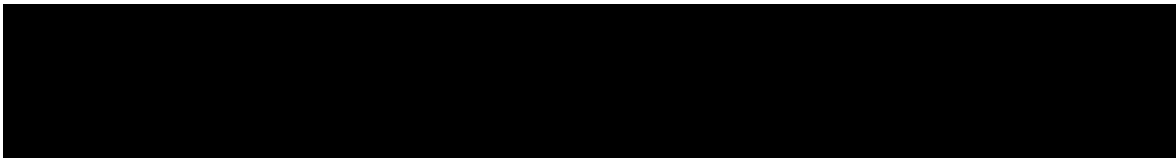
10.5.7 Patient-reported outcomes

Not applicable.



10.7 Interim analysis

No interim analysis is planned for this study.



10.8 Sample size calculation

The planned sample size of 30 is determined based on the accuracy of estimated total-group response rate at the end of 3 months.

The response rate is the proportion of responders, where responders are defined as patients with the reduction of mean GH levels to $< 2.5 \mu\text{g/L}$ and normalization of IGF-1. The response rates at 20 mg, 40mg and 60mg in [CSOM230C2110] were comparable (30% at 20mg, 41.7% at 40mg, and 38.5% at 60mg). Furthermore, the dose of pasireotide LAR will be adjusted according to efficacy and safety. It is considered, therefore, that the efficacy of pasireotide LAR can be evaluated more appropriately based on the response rate of all groups combined. In this study, based on the results from CSOM230C2110, the expected total-group response rate will be at least 30%.

In [CSOM230C2305], patients inadequately controlled with 12 month octreotide LAR study treatment were crossed over to pasireotide LAR. The response rate at 3 months after crossover was 17.3% (two-sided 95% CI: [9.8%, 27.3%]). Since a large number of patients who enroll to this study are assumed to be inadequately controlled with octreotide LAR treatment, a clinically meaningful minimum response rate is set as 10% based on the lower limit of two-sided 95% CI, 9.8%.

The expected drop out rate is 10% based on [CSOM230C2305]. The patients with missing values of mean GH levels or IGF-1 at the assessment at 3 months of study treatment or who discontinue prior to the assessment at 3 months of study treatment will be considered as non-responders.

Under these assumptions, the expected total-group response rate adjusted by the expected drop out rate is 27%. The sample size of 30 can demonstrate that the lower limit of the Clopper-Pearson exact two-sided 90% CI for the total-group response rate is not less than the clinically meaningful response rate, 10%.

10.9 Power for analysis of key secondary variables

Not applicable.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

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

11.2 Responsibilities of the investigator and IRB/IEC/REB

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

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their eCRFs.

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

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

Additional consent form

Not applicable.

11.4 Discontinuation of the study

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

11.5 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. 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 subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

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

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

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

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

11.7 Confidentiality of study documents and patient records

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

11.8 Audits and inspections

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

11.9 Financial disclosures

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

12 Protocol adherence

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

12.1 Amendments to the protocol

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

13 References (available upon request)

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14 Appendices

Appendix 1: Instructions for use

1 Procedure for pasireotide LAR 20 mg dosage strength

For preparation of the microparticle powder suspension for injection, the standard vehicle for microparticles has to be taken to reconstitute the suspension in the 6R vials.

- Take one (1) drug product vial with the following label
Project name: pasireotide LAR
Form: MPVI
Dosage: 20 MG/VIAL
- Remove the transparent flip-off cap from the vial.
- Take one vehicle ampoule and break off the upper part.
- Withdraw the content of the vehicle ampoule with the **18 G (min 50 mm length)** needle and e.g. a 3 ml syringe.
- Remove air bubbles by pushing the piston and adjust the volume to 2 ml.
- Inject 2 ml of vehicle into the vial containing the powder (20mg).
- Shake the vial **up and down** at least 30 seconds in order to get a homogenous suspension.
- Withdraw the whole volume of suspension from the vial with the same **18 G (min 50 mm length)** needle and e.g. a 3 ml syringe.
- Change the needle with a new **20 G** needle for i.m. injection.
- Remove air bubbles by pushing the piston.
- Immediately, inject the whole volume of suspension intra-muscularly to the patient.

2 Procedure for pasireotide LAR 40 mg dosage strength

For preparation of the microparticle powder suspension for injection, the standard vehicle for microparticles has to be taken to reconstitute the suspension in the 6R vials.

- Take one (1) drug product vial with the following label
Project name: pasireotide LAR
Form: MPVI
Dosage: 40 MG/VIAL
- Remove the transparent flip-off cap from the vial.
- Take one vehicle ampoule and break off the upper part.
- Withdraw the content of the vehicle ampoule with **18 G (min 50 mm length)** needle and the e.g. a **3 ml syringe**.
- Remove air bubbles by pushing the piston and adjust the volume to 2 ml.
- Inject 2 ml of vehicle into the vial containing the powder (40 mg).
- Shake the vial **up and down** at least 30 seconds in order to get a homogenous suspension.
- Withdraw the whole volume of suspension from the vial with the same **18 G (min 50 mm length)** needle and the e.g. a **3 ml syringe**.

- Change the needle with a new 20 G needle for i.m. injection
- Remove air bubbles by pushing the piston.
- Immediately, inject the whole volume of suspension intra-muscularly to the patient.

3 Procedure for pasireotide LAR 60 mg dosage strength

For preparation of the microparticle powder suspension for injection, the standard vehicle for microparticles has to be used to reconstitute the suspension in the 6R vials.

- Take one (1) drug product vials with the following label
Project name: pasireotide LAR
Form: MPVI
Dosage: 20 MG/VIAL
- Take one (1) additional drug product vial with the following label
Project name: pasireotide LAR
Form: MPVI
Dosage: 40 MG/VIAL
- Remove the transparent flip-off cap from the vials.
- Take one vehicle ampoule and break off the upper part.
- Withdraw the content of the vehicle ampoule with the **18 G (min 50 mm length)** needle and the 3 ml syringe.
- Remove air bubbles by pushing the piston and adjust the volume to 2 ml.
- Inject 2 ml of vehicle into the first vial containing the powder (20mg).
- Shake the vial **up and down** for 30 seconds in order to get a homogenous suspension.
- Withdraw the whole volume of suspension from the vial with the **18 G (min 50 mm length)** needle and the **3 ml syringe**.
- Inject the whole volume of suspension into the second vial (40mg)
- Shake the vial **up and down** at least 30 seconds in order to get a homogenous suspension.
- Withdraw the whole volume of suspension from the vial with the **18 G (min 50 mm length)** needle and e.g. a **3 ml syringe**.
- Change the needle with a new **20 G** needle i.m. injection
- Remove air bubbles by pushing the piston.
- Immediately, inject the whole volume of suspension intra-muscularly to the patient

Appendix 2: Medications known to be associated with QT interval prolongation

The following list of drugs is generally recognized to have a possible association with QT prolongation. This list is not considered to be all inclusive and any questions regarding the QT prolongation potential should be discussed with the Novartis Medical Monitor.

Drugs that are generally accepted by the QTdrugs.org Advisory Board of the Arizona CERT to have a risk of causing torsade de pointes are listed below.

| Generic Name | Brand Name | Class |
|------------------|-------------|---|
| Bepidil | Vasacor® | Anti-anginal / heart pain |
| Amiodarone | Cordarone® | Anti-arrhythmic / abnormal heart rhythm |
| Amiodarone | Pacerone® | Anti-arrhythmic / abnormal heart rhythm |
| Disopyramide | Norpace® | Anti-arrhythmic / abnormal heart rhythm |
| Dofetilide | Tikosyn® | Anti-arrhythmic / abnormal heart rhythm |
| Ibutilide | Corvert® | Anti-arrhythmic / abnormal heart rhythm |
| Procainamide | Pronestyl® | Anti-arrhythmic / abnormal heart rhythm |
| Procainamide | Procan® | Anti-arrhythmic / abnormal heart rhythm |
| Quinidine | Cardioquin® | Anti-arrhythmic / abnormal heart rhythm |
| Quinidine | Quinaglute® | Anti-arrhythmic / abnormal heart rhythm |
| Sotalol | Betapace® | Anti-arrhythmic / abnormal heart rhythm |
| Clarithromycin | Biaxin® | Antibiotic / bacterial infection |
| Sparfloxacin | Zagam® | Antibiotic / bacterial infection |
| Erythromycin | Erythrocin® | Antibiotic;GI stimulant / bacterial infection; increase GI motility |
| Erythromycin | E.E.S.® | Antibiotic;GI stimulant / bacterial infection; increase GI motility |
| Arsenic trioxide | Trisenox® | Anti-cancer / Leukemia |
| Astemizole | Hismanal® | Antihistamine / Allergic rhinitis |
| Terfenadine | Seldane® | Antihistamine / Allergic rhinitis |
| Pentamidine | Pentam® | Anti-infective / pneumocystis pneumonia |
| Pentamidine | NebuPent® | Anti-infective / pneumocystis pneumonia |
| Probucol | Loelco® | Antilipemic / Hypercholesterolemia |
| Chloroquine | Aralen® | Anti-malarial / malaria infection |
| Halofantrine | Halfan® | Anti-malarial / malaria infection |
| Domperidone | Motilium® | Anti-nausea / nausea |
| Mesoridazine | Serentil® | Anti-psychotic / schizophrenia |
| Thioridazine | Mellaril® | Anti-psychotic / schizophrenia |
| Haloperidol | Haldol® | Anti-psychotic / schizophrenia, agitation |
| Pimozide | Orap® | Anti-psychotic / Tourette's tics |
| Chlorpromazine | Thorazine® | Anti-psychotic/ Anti-emetic / schizophrenia/ nausea |
| Cisapride | Propulsid® | GI stimulant / heartburn |
| Levomethadyl | Orlaam® | Opiate agonist / pain control, narcotic dependence |
| Methadone | Dolophine® | Opiate agonist / pain control, narcotic dependence |
| Methadone | Methadose® | Opiate agonist / pain control, narcotic dependence |
| Droperidol | Inapsine® | Sedative;Anti-nausea / anesthesia adjunct, nausea |

Reference: qt drugs.org/medical-pros/drug-lists/drug-lists.cfm