

Clinical Development

Pasireotide / SOM230

Protocol CSOM230C2413 / NCT02354508

A phase IIIb multicenter, open-label, single arm study to evaluate the efficacy and safety of pasireotide in patients with acromegaly inadequately controlled with first generation somatostatin analogues

Authors



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List of abbreviations

AcroQoL	Acromegaly Quality of Life
ACTH	Adrenocorticotropic Hormone
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
Anti-HBc	Anti-Hepatitis B core
Anti-HCV	Anti-Hepatitis C Virus
Anti-HEV	Anti-Hepatitis E Virus
APTT	Partial Thromboplastin Time
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATC Class	Anatomical Therapeutic Chemical Classification System
ATG	Autogel
B-hCG	β-subunit of hCG gonadotropin
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CPK	Creatine Phosphokinase
CPO	(Novartis) Country Pharma Organization
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSR	Clinical study report
CSR addendum	An addendum to Clinical Study Report (CSR) that captures all the additional information that is not included in the CSR
CTCAE	Common Toxicity Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DM	Diabetes Mellitus
DMC	Data Monitoring Committee
DS&E	Drug Safety and Epidemiology
EBV	Epstein Barr Virus
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GH	Growth Hormone
GIP/GLP	Gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1
HbA1C	Hemoglobin A1c
Hbs-Ag	Hepatitis B surface-Antigen
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
HRQoL	Health Related Quality of Life
i.m.	Intramuscular
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IGF	Insulin-like Growth Factor

IgM	Immunoglobulin M
IMS	Integrated Medical Safety
IRB	Institutional Review Board
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
ITT	Intention To Treat
IUD	Intrauterine Device
IUS	Intrauterine System
LAR	Long Acting Release
LDH	Lactic Dehydrogenase
LDL	Low Density Lipoprotein
LFT	Liver Function Testing
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-CTCAE v.4.03	National Cancer Institute-Common Toxicity Criteria Adverse Event version 4.03
OGTT	Oral Glucose Tolerance Test
PCR	Polymerase Chain Reaction
PHI	Protected Health Information
PK/PD	Pharmacokinetic/Pharmacodynamic
PRL	Prolactin
PRO	Patient Reported Outcomes
PT	Prothrombin Time
PTT	Partial Thromboplastin time
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
REB	Research Ethics Board
s.c.	Subcutaneous
SAE	Serious Adverse Event
SC	Steering Committee
SOP	Standard Operating Procedure
SSA	Somatostatin analogues
sst	somatostatin receptor subtype
TdP	Torsades de pointes
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit Normal
γ-GT	Gamma-Glutamyltransferase

Glossary of terms

Assessment	A procedure used to generate data required by the study
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Patient Number	A unique identifying number assigned to each patient/subject/healthy volunteer 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, unless the patient will be followed for progression and/or survival
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Treatment group	A treatment group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. Cohorts are not expanded, new cohorts are enrolled.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

Protocol summary:

Protocol number	CSOMC2413
Title	A phase IIIb multicenter, open-label, single arm study to evaluate the efficacy and safety of pasireotide in patients with acromegaly inadequately controlled with first generation somatostatin analogues
Brief title	Study of efficacy and safety of pasireotide LAR in patients with inadequately controlled acromegaly
Sponsor and Clinical Phase	Novartis, Phase IIIb
Investigation type	Drug
Study type	Interventional
Purpose and rationale	To evaluate the efficacy and safety of pasireotide, a second generation somatostatin analogue with a broader affinity to sst receptors, in patients with in adequately controlled acromegaly after a minimum of 3 months with high doses of first generation somatostatin analogues.
Primary Objective(s)	Primary Objective To evaluate the efficacy of pasireotide LAR in patients with acromegaly who are inadequately controlled with currently available somatostatin analogues, as measured by the proportion of patients with GH <1µg/L and IGF-1 <ULN at week 36 overall and by mGH level at screening. Supporting Analysis for Primary To assess the proportion of patients achieving GH <1µg/L and IGF-1 <ULN at week 36 by GH level at screening.
Secondary Objectives	Core Phase To assess the changes in mean GH from study baseline to week 36. To assess the changes in standardized IGF-1 from study baseline to week 36. To assess the proportion of patients achieving GH <1 µg/L and IGF-1 <ULN at weeks 12 and 24 overall and by GH level at screening To assess the proportion of patients achieving GH <1µg/L at weeks 12, 24 and 36, overall and by GH level at screening To assess the proportion of patients achieving IGF-1 levels <ULN at weeks 12, 24 and 36 To evaluate the tolerability and safety profile of pasireotide LAR To evaluate the effect of pasireotide LAR on HRQoL and signs and symptoms of acromegaly from baseline to weeks 12, 24 and 36 Extension Phase To assess the proportion of patients achieving GH <1 µg/L and IGF-1 <ULN overall and by GH level at screening at weeks 48, 60 and 72 during the treatment with pasireotide LAR monotherapy To evaluate the long term tolerability and safety profile of pasireotide LAR To evaluate the long term effect of pasireotide LAR on HRQoL and signs and symptoms of acromegaly, from baseline and week 36 to week 72
Study design	Group 1 – Patients treated with octreotide LAR 30mg from the countries where octreotide LAR 40mg is approved for the treatment of acromegaly at the time of screening – Patients participate in the run-in phase. Run-In phase (Screening to Baseline) Patients will start treatment with octreotide LAR 40 mg every 4 weeks. Patients who have not achieved biochemical control after 3 injections can be enrolled in the study. Core Phase (Baseline to week 36) Patients will start treatment on pasireotide LAR 40 mg every 4 weeks until week 32. A mean GH value and IGF-1 value will be assessed every 12 weeks until week 36. The dose can be adjusted after the evaluation of biochemical control. During

	<p>the core phase any acromegaly concomitant medication is prohibited.</p> <p>Extension Phase (week 36 to week 76) Patients will receive the same dose of pasireotide LAR at week 36, which is the first dose of study medication in the extension phase. At week 40 the dose can be adjusted and acromegaly concomitant medication can be added to the treatment if, patients remain uncontrolled. Patients will receive pasireotide LAR 40mg/60mg until week 68 for a total of 32 weeks in the extension phase. A mean GH value and IGF-1 value will be assessed every 12 weeks until week 72.</p> <p>Safety follow-up After discontinuation or completion of study treatment, all patients will be followed for safety 8 weeks after the last study drug administration.</p> <p>Group 2 – Patients treated with octreotide 30 mg from countries where octreotide 40mg has NOT been approved for the treatment of acromegaly at screening or patients treated with octreotide 40mg or lanreotide 120mg - Patients who do not have the run-in phase.</p> <p>Core Phase (Baseline to week 36) Same procedure to be followed as Group1</p> <p>Extension Phase (week 36 to week 76) Same procedure to be followed as Group1</p> <p>Safety follow-up Same procedure to be followed as Group1</p>
Population	The eligible patient population will consist of inadequately controlled acromegalic patients with first generation somatostatin analogues. The study will enroll a total number of 112 patients.
Inclusion criteria	<p>Patients eligible for inclusion in this study have to meet all of the following criteria:</p> <ol style="list-style-type: none"> 1. Written informed consent must be obtained prior to any screening procedures 2. Male and female patients ≥ 18 years of age 3. Patients with confirmed diagnosis of inadequately controlled acromegaly as evidenced by the following: <ul style="list-style-type: none"> • A mean GH concentration of a 5-point profile over a 2-hour period $\geq 1 \mu\text{g/L}$ and sex- and age-adjusted IGF-1 $>1.3 \times \text{ULN}$ 4. Patients treated with high doses of octreotide LAR (30 mg or 40 mg) or lanreotide ATG (120 mg) given as monotherapy for at least 3 months prior to screening (Visit 1) <ul style="list-style-type: none"> • Note: Patients currently being treated with octreotide LAR 30mg from countries where the 40 mg dose is approved at the time of screening will start a run- in phase which they will receive the 3 injections of octreotide LAR 40 mg before being evaluated for eligibility for the core phase of the study
Exclusion criteria	<p>Patients eligible for this study must not meet any of the following criteria:</p> <ol style="list-style-type: none"> 1. Concomitant treatment with other medications known to reduce GH and or IGF-1, other than octreotide LAR or lanreotide ATG, unless it discontinued 3 months prior to visit 1 (screening) 2. Patients with compression of the optic chiasm causing any visual field defect that requires surgical intervention 3. Diabetic patients with poor glycaemic control as evidenced by HbA1c $>8\%$ at visit 1 (screening) 4. Patients who are hypothyroid and not on adequate replacement therapy 5. Patients with symptomatic cholelithiasis and acute or chronic pancreatitis 6. Patients with clinically significant valvular disease 7. Patients with risk factors for torsade de pointes, i.e. patients with a baseline QTcF >450 ms in males, and >460 ms in females 8. Hypokalaemia, hypomagnesaemia, uncontrolled hypothyroidism, family history of long QT syndrome or concomitant medications with known risk of TdP. Drugs

with possible risk of TdP should be avoided whenever feasible.

9. Patients who have congestive heart failure (NYHA Class III or IV), unstable angina, sustained ventricular tachycardia, clinically significant bradycardia, advanced heart block, history of acute MI less than one year prior to study entry or clinically significant impairment in cardiovascular function.

10. Concomitant disease(s) that could prolong the QT interval such as autonomic neuropathy (caused by diabetes or Parkinson's disease), HIV, cirrhosis, uncontrolled hypothyroidism or cardiac failure

11. Patients with liver disease such as cirrhosis, chronic active hepatitis, or chronic persistent hepatitis, or patients with ALT/AST > 2.0 X ULN, serum bilirubin >2.0 X ULN

12. Presence of Hepatitis B surface antigen (HbsAg) or Hepatitis C antibody test (anti-HCV)

13. Patients with serum creatinine >2.0 X ULN

14. Patients with WBC <3 X 10⁹/L; Hb 90% < LLN; PLT <100 X 10⁹/L

15. Patients with the presence of active or suspected acute or chronic uncontrolled infection

16. Patients who have undergone major surgery/surgical therapy for any cause within 4 weeks prior to visit 1 (screening)

17. Patients with active malignant disease within the last five years (with the exception of basal cell carcinoma or carcinoma in situ of the cervix)

18. 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)

19. History of syncope or family history of idiopathic sudden death

20. History of immunocompromise, including a positive HIV test result (ELISA and Western blot). A HIV test will not be required; however, previous medical history will be reviewed

21. Known hypersensitivity to somatostatin analogues or any other component of the pasireotide LAR

22. Patients who have a history of alcohol or drug abuse in the 6 month period prior to receiving pasireotide

23. Patients who have given a blood donation (of 400 ml or more) within 2 months before receiving pasireotide

24. Patients who have participated in any clinical investigation with an investigational drug within 1 month prior to dosing

25. Patients with any current or prior medical condition that, in the judgment of the investigator may interfere with the conduct of the study or the evaluation of the study results

26. 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.

27. Sexually active males unless they use a condom during intercourse while taking drug and for 3 months following last dose of pasireotide 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.

28. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.

29. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and 3 months following the last dose of pasireotide. Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 months prior to screening). For female subjects on the study the vasectomized male partner should be the sole partner for that

	<p>subject.</p> <ul style="list-style-type: none"> • Combination of any two of the following (a+b or a+c, or b+c): <ul style="list-style-type: none"> a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. b. Placement of an intrauterine device (IUD) or intrauterine system (IUS) c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository <p>In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.</p> <p>Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.</p>
Investigational and reference therapy	pasireotide LAR 40mg and 60mg, octreotide LAR 40mg
Efficacy assessments	<ul style="list-style-type: none"> • A 5-point GH • IGF1 • Acromegaly symptoms • Health-related Quality of Life
Safety assessments	<ul style="list-style-type: none"> • Physical examination • Vital signs • Laboratory evaluations (hematology, clinical chemistry, liver function testing, coagulation, urinalysis) • Pregnancy • Gallbladder ultrasound • Cardiac assessments
Other assessments	NA
Data analysis	<p>The primary variable is the proportion of patients who achieved GH < 1μg/L and IGF-1 < ULN at week 36. This proportion will be provided along with its asymptotic (or exact, depending on the sample size) 95% CI. Secondary objectives which are measured by proportions will be similarly reported. Descriptive summaries of actual and percentage change in GH, actual and percentage change in standardized IGF-1, from study baseline to week 36 values will be provided. Change in standardized scores as measured by HRQoL and signs and symptoms of acromegaly from baseline and week 36 to week 72 will be provided.</p>
Key words	acromegaly, pasireotide LAR, octreotide LAR, 5-point GH, IGF-1

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Acromegaly is a rare growth disorder characterized by a clinical syndrome resulting primarily from the effects of excess growth hormone (GH) and insulin-like growth factor 1 (IGF-1) on various organ systems. Acromegaly is caused by a GH-secreting pituitary adenoma in more than 90% of patients. The prevalence of acromegaly is estimated to be 40 to 70 cases per million, with an annual incidence of 3 to 4 new cases per million ([Holdaway and Rajasoorya 1999](#)). However, recent studies suggest that pituitary adenomas may be more prevalent than previously thought, and that the prevalence of acromegaly may be well over 100 cases per million ([Rosario 2011, Daly et al 2006](#)).

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

The therapeutic goals in acromegaly are to reduce mortality to the expected age and sex adjusted rates by using treatments that remove the tumor mass and/or control its growth and restore GH secretion and action to normal. In the past, the biochemical goals of therapy were to reduce the circulating IGF-1 levels to normal for age and sex and to reduce serum GH concentrations to <2.5 µg/L (mean GH concentration of a 5-point profile within a 2-hour time period) or to less than 1 µg/L after an oral glucose load ([Giustina et al 2000](#)). Current guidelines recommend GH levels <1 µg/L and normalization of IGF-1 as biochemical goals of therapy ([Melmed et al 2010](#)).

Treatment modalities for acromegaly include surgery, radiotherapy or treatment with drugs.

Surgery: transphenoidal surgery is the most frequently recommended treatment however surgical effectiveness varies depending on expertise in pituitary surgery, on the size and extension of the anatomic mass, and the preoperative levels of GH. 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 throughout their lifespan 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 medications. 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 drugs in rare cases as primary treatment. It is usually reserved 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 over a 2-year timeframe, although late effects can occur in some cases. Radiation therapy causes 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: the medical treatment options for acromegaly include somatostatin analogues, growth hormone antagonists and dopamine agonists.

Somatostatin analogues have proven to be safe, well-tolerated and effective and are the medical treatment of choice for patients with acromegaly. The currently marketed somatostatin analogues are octreotide (Sandostatin®) and lanreotide (Somatuline®). Octreotide has been available for over 20 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 treatment(s) and other study treatment(s)

1.2.1 Overview of pasireotide (SOM230)

Pasireotide (SOM230) is a cyclohexapeptide, SSA with the following chemical name: (2-Aminoethyl)carbamic acid (2R,5S,8S,11S,14R,17S,19aS)-11-(4-aminobutyl)-5-benzyl-8-(4-benzyloxybenzyl)-14-(1H-indol-3ylmethyl)-4,7,10,13,16,19-hexaoxo-17-phenyloctadecahydro-3a,6,9,12,15,18-hexaazacyclopentacyclooctadeen-2-yl ester, di[(S)-2aminosuccinic acid] salt. Like natural somatostatin and other SSAs, pasireotide exerts its pharmacological activity via binding to somatostatin receptors (sst.). Somatostatin is an endogenous peptide that modulates a number of exocrine and endocrine secretions. There are five known somatostatin receptors: sst1, 2, 3, 4 and 5 as outlined in Table 1-1. When compared to octreotide, pasireotide has a binding affinity which is 30-40 times greater for sst1 and sst5, 5 times greater for sst3, and a comparable affinity for sst2 ([Schmid and Brueggen 2012](#)). Somatostatin receptors are expressed in different tissues under normal physiological conditions as well as in many solid tumors, especially in neuroendocrine tumors where hormones are excessively secreted, e.g. acromegaly, gastroenteropancreatic neuroendocrine tumor (GEP/NET) and Cushing's disease ([Freda 2002](#), [Oberg et al 2004](#) and [Van der Hoek et al 2005](#)). A detailed summary of available preclinical data is provided in the current [Investigator's Brochure].

Table 1-1 Binding profiles for octreotide and pasireotide at hsst1-5 (IC50, mol/L)

Compound	sst1	sst2	sst3	sst4	sst5
Octreotide acetate (SMS995)	2.8x10 ⁻⁷	3.8x10 ⁻¹⁰	7.1x10 ⁻⁹	>10 ⁻⁶	6.3x10 ⁻⁹
Pasireotide (SOM230)	9.3x10 ⁻⁹	1.0x10 ⁻⁹	1.5x10 ⁻⁹	>10 ⁻⁶	1.6x10 ⁻¹⁰
Ratio of IC ₅₀ :octreotide acetate/pasireotide (SMS995/SOM230)	30	0.4	5	--	39

1.2.1.1 Non-clinical experience

Preclinical data on binding affinity and functional activity in vitro and efficacy on hormone secretion in vivo have been obtained with the s.c. formulation in rats, dogs, mice and monkeys. Long-term in vivo studies performed using drug application by osmotic mini-pumps (Bruns 2002, Weckbecker 2002) have shown not only that the inhibitory effect of pasireotide was stronger, but also that there was less response escape (Bruns 2002) and (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.

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

1.2.1.2 Clinical experience

The clinical development program for pasireotide has focused on endocrine-related pathologies. Two formulations of pasireotide are currently in development: an immediate release formulation for subcutaneous (s.c.) injection and a long-acting release (LAR) formulation for i.m. injection. These formulations have been characterized by Phase 1 studies in healthy volunteers, and Phase 1 - 3 studies in patients with acromegaly, Cushing's disease, and gastroenteropancreatic neuroendocrine tumors.

The pasireotide s.c. formulation (Signifor®) is currently approved in more than 50 countries worldwide for the treatment of Cushing's disease.

The efficacy and safety of pasireotide LAR in acromegaly are primarily derived from two large, randomized Phase 3 studies comparing pasireotide LAR with active controls (superiority design):

- Study [SOM230C2305] compared pasireotide LAR with octreotide LAR in medically naïve patients with active acromegaly. In this study, pasireotide LAR was shown to be significantly superior to octreotide LAR for the treatment of acromegaly in medically naïve patients in terms of biochemical control (GH < 2.5 µg/L and normalization of IGF-1 levels) (31.3% vs. 19.2%; p-value 0.007), providing higher response rate in both de novo patients and in patients with prior pituitary surgery (25.7% vs. 17.3% in de novo patients; 39.4% vs. 21.8% in post-surgical patients). Pasireotide LAR was as effective as octreotide LAR in reducing tumor volume, improving acromegaly symptoms and ring size, and quality of life [CSOM230C2305].
- Study [SOM230C2402] compared double-blind pasireotide LAR 40 mg and pasireotide LAR 60 mg with open-label octreotide LAR or lanreotide ATG – active control – in patients with inadequately controlled acromegaly. This study showed that both pasireotide LAR doses (40 mg and 60 mg) are superior to active control (octreotide LAR 30 mg or lanreotide ATG 120 mg). The proportion of responders at Week 24 was significantly higher with pasireotide LAR 40 mg (15.4%, 95% CI 7.63, 26.48) and pasireotide LAR 60 mg (20.0%, 95% CI 11.10, 31.77) than in patients who continued their previous treatment (0%) (p=0.0006 and <0.0001 for pasireotide LAR 40 mg and 60 mg, respectively). Both pasireotide doses were superior to active control in normalizing IGF-1 levels and in

reducing GH to <2.5 µg/L. The proportion of patients with a reduction of GH to <2.5 µg/L at Week 24 was highest in the pasireotide LAR 60 mg arm (43.1%), followed by the pasireotide LAR 40 mg arm (35.4%), and the active control arm (13.2%). The proportion of patients who achieved normalization of IGF-1 at Week 24 (key secondary efficacy variable) was significantly higher in both pasireotide arms (24.6% and 26.2% responders) compared to the active control arm (zero responders)

The safety of pasireotide has been well characterized in 491 patients with acromegaly (419 patients using the LAR formulation, and 72 patients using the s.c. formulation). In addition, pasireotide s.c. and LAR formulations have been used in over 750 other subjects including healthy volunteer and special safety studies. The safety findings in patients with acromegaly are in line with expected pharmacodynamic effects of pasireotide, based on both preclinical and clinical experience, and are consistent with the known side effects of approved SSAs (with the exception of an increased incidence and magnitude of hyperglycemia)

A detailed summary of the clinical data (including safety and PK) is provided in the current [Investigator's Brochure].

2 Rationale

2.1 Study rationale and purpose

Pasireotide (SOM230) is a second generation SSA with a higher affinity to a greater number of somatostatin receptors compared to octreotide and lanreotide, which results in improved efficacy in acromegaly. Pituitary GH-secreting tumors primarily express SSTR2 and 5 (and to a lesser extent SSTR1 and 3). The currently available SSAs octreotide and lanreotide have high affinity for SSTR2, and low affinity for the remaining receptor subtypes. Although SSTR2 is considered the pivotal receptor subtype for regulation of GH secretion, its expression is variable and this may at least in part explain resistance or partial response to octreotide or lanreotide therapy observed in some patients. Recent data suggest that approximately 50% of the patients are not biochemically controlled with currently available SSAs ([Carmichael et. al 2014](#)). In a recently completed phase III study in medically naive acromegalic patients, the largest in this population, 19% of patients treated with octreotide LAR achieved biochemical control after one year of treatment.

Results of clinical studies currently available with pasireotide indicate that it is a safe and effective treatment in patients with acromegaly. The purpose of this study is to evaluate the efficacy and safety of pasireotide LAR, in patients with acromegaly who are inadequately controlled after a minimum of 3 months with maximal approved doses of first generation somatostatin analogues (octreotide LAR 30 mg or 40 mg – depending on the country - or lanreotide ATG 120mg). The recently completed SOM230C2402 study in biochemically uncontrolled patients after at least 6 months of treatment with high doses of octreotide LAR or lanreotide ATG showed that no further benefit was achieved when this therapy was continued with patients achieving neither biochemical control nor normal IGF-1. Therefore, an earlier treatment change to pasireotide LAR might be beneficial for these patients.

In addition, a new consensus has been reached on the definition of controlled acromegaly: GH<1.0 µg/L in association with normal IGF-I levels ([Giustina et al 2014](#)). Therefore, the

new study will enrol patients that satisfy the new criteria of uncontrolled acromegaly – GH \geq 1.0 μ g/L and IGF-I $>$ 1.3xULN - and it will provide data not only in the patients with a GH $>$ 2.5 μ g/L but also, for the first time, in the patients with a GH level between 1.0 and 2.5 μ g/L that are known to represent a large group of patients with inadequately controlled acromegaly.

2.2 Rationale for the study design

The study is an open-label, single-arm; multi-centre international study to evaluate the safety and the efficacy of pasireotide LAR in patient with inadequately controlled acromegaly after a minimum of 3 months with high doses of the first generation somatostatin analogues.

A single-arm, open-label study design was chosen since the objective of this study is to obtain further data of the efficacy and safety of pasireotide LAR in patients with acromegaly, but not as confirmation of efficacy. Efficacy of pasireotide in patients not controlled with other somatostatin analogues was already demonstrated in Study C2402, a double-blinded controlled study, in which patients randomized to the active control (octreotide LAR 30mg or lanreotide ATG 120mg) did not achieve biochemical control with further treatment whereas patients randomly allocated to pasireotide LAR 40 mg or 60 mg were able to achieve biochemical control for the very first time. Additionally, the natural history of the disease is well understood and placebo effects on efficacy evaluations are negligible.

The primary objective of the study was chosen based on the new published criteria for diagnosis and management of acromegaly (Giustina et al 2014). Elevated GH and IGF-1 levels are predictors of mortality, and lowering GH and normalizing IGF-1 results in mortality rates similar to those expected in the general population. The definition of a safe GH level was updated, due to the new more sensitive and specific assays. This new guideline recommends reducing GH to levels as close to normal as possible. According to this consensus document optimal disease control is now defined as IGF-1 level in the age-adjusted normal range and a GH level less than 1.0 μ g/L. This data will complement the results obtained in study C2402, where patients achieving the previous definition of biochemical control (i.e. GH levels $<$ 2.5 μ g/L and normalization of IGF-1) were reported.

2.3 Rationale for dose and regimen selection

The pasireotide LAR dose for acromegaly patients is based on the study CSOM230C2305. It was a multi-center, randomized, blinded study to assess the safety and efficacy of pasireotide LAR vs. octreotide LAR in patients with active acromegaly. The results of the study demonstrated that pasireotide LAR 40 mg every 28 days is superior to octreotide LAR 20 mg every 28 days in providing biochemical control in patients with medically naïve acromegaly i.e., suppression of GH levels to $<$ 2.5 μ g/L and normalization of IGF-1 [CSOM230C2305]. Patients enrolled in this study will start with pasireotide LAR 40 mg every 28days.

Study [CSOM230C2402] demonstrated that both doses of pasireotide LAR 40mg and 60 mg are efficacious in patients inadequately controlled on octreotide LAR and lanreotide ATG.

Based on these data, patients should be evaluated for clinical benefit 3 months (84 days) after the start of pasireotide LAR 40 mg (i.m.) therapy. A dose increase to 60 mg every 28 days will be mandated after 12 weeks of pasireotide LAR treatment if adequate levels of GH and

IGF-1 are not observed with the 40 mg dose (no reduction of mean GH level to < 1.0 μ g/L and no decrease of IGF-1 to within normal limits (age and sex related) and provided there are no safety concerns.

Management of suspected adverse reactions may require temporary dose reduction of pasireotide LAR. Dose reduction by decrements of 20 mg every 28 days is recommended. Dose increase and dose reduction is to be based on investigator's assessment of risk and benefit for the patient.

In the case of octreotide LAR, in order to be enrolled in the study, patients should have been treated with 30 or 40 mg for at least three months and not achieved biochemical control. Octreotide LAR 30mg has been approved and available for over 20 years: octreotide LAR 40mg is not approved/available in all countries. Patients enrolled in countries where the 40mg dose is approved, must be treated with this dose prior to enrollment or during the run-in phase of the study.

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		Refer to Section 10.4
To evaluate the efficacy of pasireotide LAR in patients with acromegaly who are inadequately controlled with maximal approved doses of currently available somatostatin analogues, as measured by the proportion of patients with GH <1µg/L and IGF-1 <ULN at week 36	Proportion of patients who achieved GH <1µg/L and IGF-1 <ULN at week 36.	
Supporting Analysis for Primary		Refer to Section 10.4.4
To assess the proportion of patients achieving GH <1µg/L and IGF-1 <ULN at week 36 by GH level at screening.	Proportion of patients who achieved GH <1µg/L and IGF-1 <ULN at week 36 in patients having GH level at screening between 1 µg/L and 2.5 µg/L, and in patients having GH level at screening >2.5 µg/L	
Secondary- core phase		Refer to Section 10.5.1
To assess the changes in mean GH from study baseline to week 36	Changes in mean GH from study baseline to week 36.	
To assess the changes in standardized IGF-1 from study baseline to week 36	Changes in standardized IGF-1 from study baseline to week 36.	
To assess the proportion of patients achieving GH <1 µg/L and IGF-1 <ULN at weeks 12 and 24 overall and by GH level at screening	Proportion of patients who achieved GH <1µg/L and IGF-1 <ULN at week 12 and 24 overall and by GH level at screening.	
To assess the proportion of patients achieving GH <1µg/L at weeks 12, 24 and 36, overall and by GH level at screening	Proportion of patients who achieved GH <1µg/L at week 12, 24 and 36 overall and by GH level at screening.	
To assess the proportion of patients achieving IGF-1 levels <ULN at weeks 12, 24 and 36	Proportion of patients who achieved IGF-1 <ULN at week 12, 24 and 36.	
To evaluate the tolerability and safety profile of pasireotide LAR	Toxicity will be assessed using the National Cancer Institute-Common Toxicology Criteria Adverse Events version 4 (NCI-CTCAE v.4.03) and for laboratory assessments that include biochemistry, hematology, urinalysis; special safety assessments that include the regular monitoring and recording of blood glucose, insulin, HbA1c, GH and IGF-1, thyroid and liver	

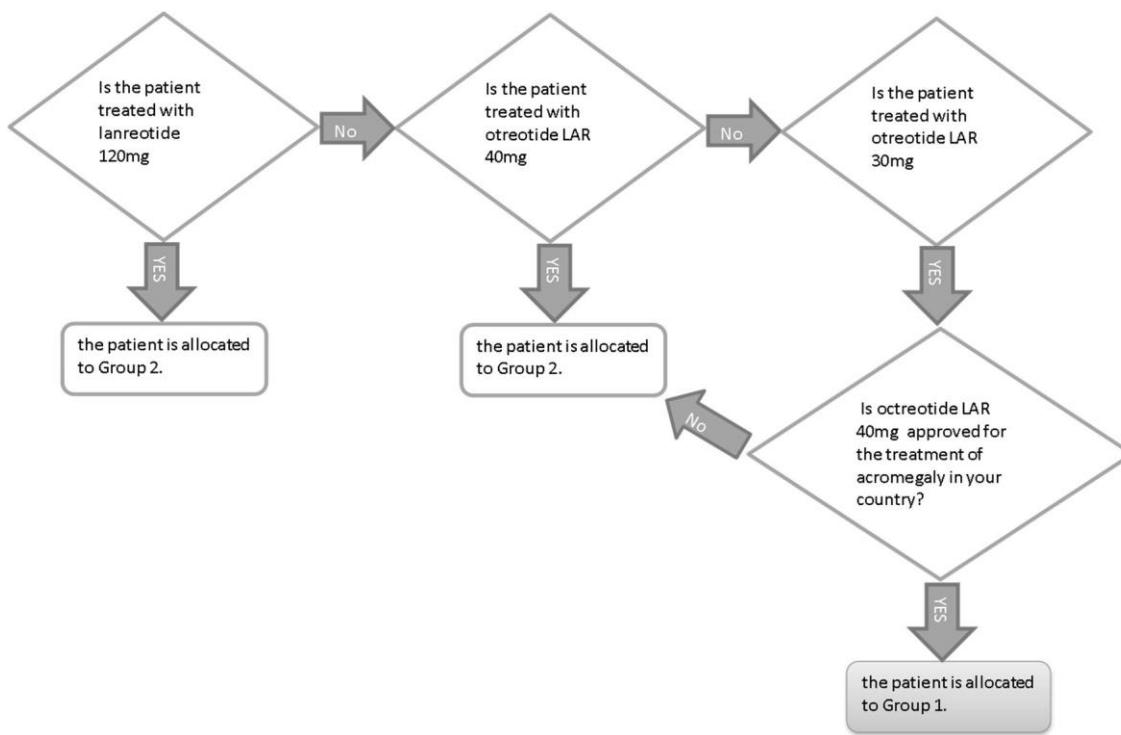
Objective	Endpoint	Analysis
	function tests, gallbladder examinations and ECGs. Concomitant medications/Significant nondrug therapies will be assessed from study enrollment until the safety follow-up.	
To evaluate the effect of pasireotide LAR on HRQoL and signs and symptoms of acromegaly from baseline to weeks 12, 24 and 36	Change in scores as measured by AcroQoL, EQ-5D-5L and signs and symptoms of acromegaly from baseline to weeks 12, 24 and 36	
Secondary – extension phase		
To assess the proportion of patients achieving IGF-1 <ULN at weeks 48, 60 and 72	Proportion of patients who achieved IGF-1 <ULN at weeks 48, 60 and 72	Refer to Section 10.5.2
To assess the proportion of patients achieving GH <1 µg/L and IGF-1 <ULN at weeks 48, 60 and 72 by treatment with pasireotide LAR alone or with concomitant medications used to treat acromegaly	Proportion of patients who achieved GH <1 µg/L and IGF-1 <ULN at weeks 48, 60 and 72 by treatment with pasireotide LAR alone or with concomitant medications used to treat acromegaly	
To assess the proportion of patients achieving GH <1 µg/L at weeks 48, 60 and 72 by treatment with pasireotide LAR alone or with concomitant medications used to treat acromegaly	Proportion of patients who achieved GH <1 µg/L at weeks 48, 60 and 72 by treatment with pasireotide LAR alone or with concomitant medications used to treat acromegaly	
To evaluate the long term tolerability and safety profile of pasireotide LAR	Toxicity will be assessed using the National Cancer Institute-Common Toxicology Criteria Adverse Events version 4 (NCI-CTCAE v.4.03) and for laboratory assessments that include biochemistry, hematology, urinalysis; special safety assessments that include the regular monitoring and recording of blood glucose, insulin, HbA1c, GH and IGF-1, thyroid and liver function tests, gallbladder examinations and ECGs. Concomitant medications/Significant nondrug therapies will be assessed from study enrollment until the safety follow-up.	
To evaluate the long term effect of pasireotide LAR on HRQoL and signs and symptoms of acromegaly, from baseline and week 36 to week 72	Change in scores as measured by AcroQoL, EQ-5D-5L and signs and symptoms of acromegaly from baseline to week 72 and from week 36 to week 72.	

4 Study design

4.1 Description of study design

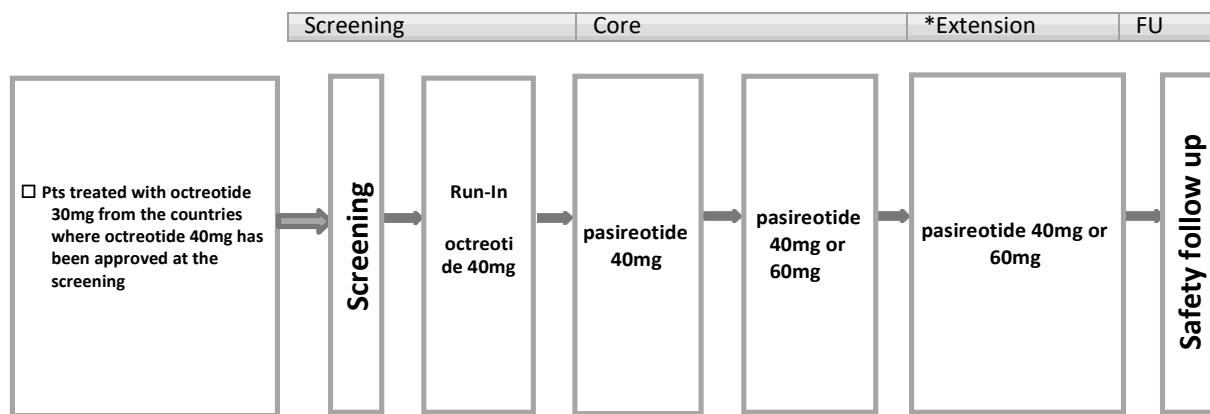
This is a phase IIIb multicenter, open-label; single arm study to evaluate the efficacy and safety of pasireotide LAR 40 mg and 60 mg in patients with inadequately controlled acromegaly with maximal doses of first generation somatostatin analogues. The study will enroll inadequately controlled patients by high doses of first-generation somatostatin analogues given for at least 3 months.

Figure 4-1 Flow Chart for Group 1 and Group 2 Patients



Group 1 – It consists of patients treated with octreotide LAR 30 mg from countries where octreotide LAR 40mg is approved for the treatment of acromegaly at the time of screening – These patients will start a run-in phase to receive 40mg octreotide before being considered eligible to enter the core treatment phase.

Figure 4-2 Study Design; Group 1



*Patients who do not achieve biochemical control at the end of the core phase (or at any time during the extension phase) will be allowed to use concomitant medications used to treat acromegaly based on the investigator's clinical judgment.

Run-In phase (Screening to Baseline)

Patients treated with octreotide LAR 30 mg who meet all inclusion criteria and no exclusion criteria will start treatment with octreotide LAR 40 mg in the run-in phase. Patients must have been treated with octreotide LAR 30 mg for at least three months before the screening visit. Patients will start treatment in the run-in phase and will receive octreotide LAR 40 mg every 4 weeks for 3 months. A mean GH value and IGF-1 value will be assessed after the third injection.

Patients who are achieving biochemical control will be considered screening failure and they will not qualify for the core phase of the study. They will continue treatment with octreotide LAR 40 mg outside the frame of this study.

Core Phase (Baseline to Visit 777)

Patients treated with octreotide LAR 40 mg in the run-in phase that meet all inclusion criteria and no exclusion criteria will be enrolled in the core phase of the study. The evaluation at the last visit of the run-in phase must be used for the eligibility assessment. Patients will start treatment with pasireotide LAR 40 mg every 4 weeks. At week 12, the mean GH value and IGF-1 value will be assessed. Patients who have not achieved biochemical control by week 12 and do not have any tolerability issues with pasireotide LAR 40 mg will have the dose increased to 60 mg. Patients who have achieved biochemical control by week 12 will maintain a dose of pasireotide LAR 40 mg. A mean GH value and IGF-1 value will be assessed every 12 weeks until Visit 777. At weeks 16 and 28, the investigator will be able to adjust the dose based on the achievement of biochemical control and drug tolerability. If tolerability issues occur, the dose can be decreased in 20 mg. Once the tolerability issue resolves, the patients should return to the dose previously received. Patients will be treated for a total of 36 weeks during the core phase. During this period any concomitant medication for the treatment of acromegaly is prohibited. Patients are required to complete a core phase completion visit 4 weeks after the last dose of pasireotide LAR is administered. Patients who discontinue from

the core phase are also required to complete the core phase completion visit 4 weeks after receiving the last pasireotide LAR dose.

Extension Phase (Visit 18 to Visit 778)

Patients who have completed all visits of core phase and have completed all the assessments at the core phase completion visit (= Visit 777) can move into the extension phase. The core phase completion visit performed at Visit 777, will also be the first visit (= Visit 18) of the extension phase. At Visit 18, the patients will receive the same dose of pasireotide LAR that they received at week 32 (= Visit 17). At week 40 (= Visit 19), the investigator will decide the treatment regimen and the pasireotide dose based on the achievement of biochemical control at Visit 777. Patients achieving biochemical control at the end of the core phase will continue pasireotide LAR monotherapy at the same dose of the core phase. Patients who are uncontrolled at the end of the core phase will continue pasireotide LAR 60 mg and they will be allowed to receive concomitant treatment with medications used to treat acromegaly based on the investigator's clinical judgment. GH and IGF-1 levels will be assessed every 12 weeks until week 72. At weeks 52 and 64, the investigator will be able to adjust the dose of pasireotide LAR and the regimen of the concomitant medication used to acromegaly based on the patients achievement of biochemical control and drug tolerability. Patients will be treated for a total of 32 weeks in the extension phase and receive the last dose of study treatment at week 68 (= Visit 26). Patients are required to complete an extension phase completion visit 4 weeks after the last dose of pasireotide LAR is administered. Patients who prematurely discontinue from the extension phase are also required to complete the extension phase completion visit 4 weeks after receiving the last dose of pasireotide LAR

Safety follow-up

After discontinuation from the study or completion of study treatment either at the core phase or extension phase of the study, all patients will be followed for safety for 8 weeks after the last study drug administration. This visit can be performed by phone, a study visit for follow-up is not mandatory.

Group 2 – It consists of patients treated with octreotide LAR 30 mg from countries where octreotide 40mg is NOT yet approved at the time of screening. This group also include patients already treated with octreotide LAR 40 mg or lanreotide ATG 120 mg. Patients should have been treated with the first generation SSAs for at least 3 months prior to screening. Eligible patients can directly enter the core treatment phase of the study. –A run-in phase is not required for this patient population.

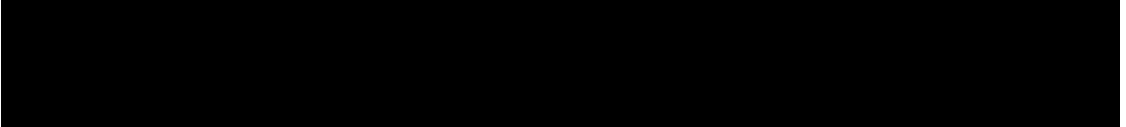
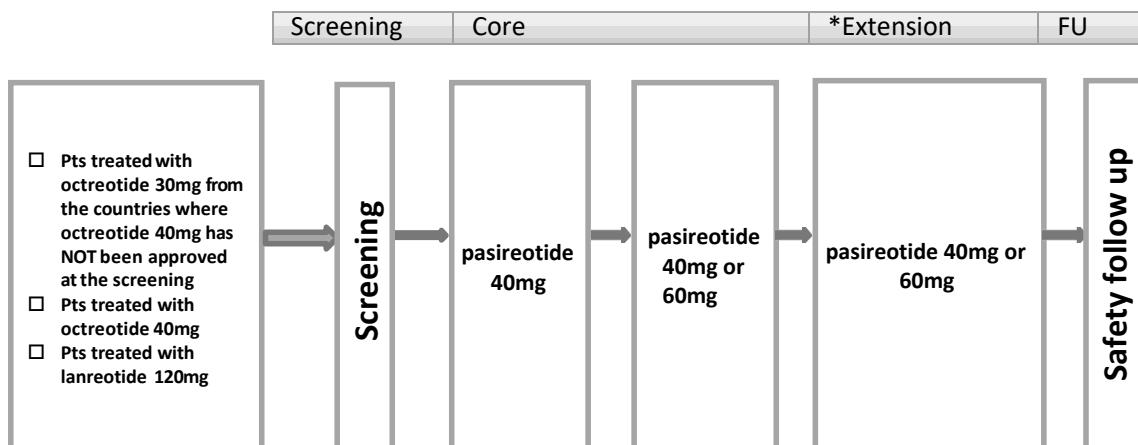


Figure 4-3 Study Design; Group 2



* Patients who do not achieve biochemical control at the end of the core phase (or at any time during the extension phase) will be allowed to use concomitant medications used to treat acromegaly based on the investigator's clinical judgment.

Core Phase (Baseline to Visit 777)

Please refer to the core phase for Group 1.

Extension Phase (Visit 18 to Visit 778)

Please refer to the extension phase for Group 1.

Safety follow-up

Please refer to Safety follow-up for Group 1.

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 will occur when all patients have completed their study completion visit and the follow up visit as per [Table 7-1](#) and [Table 7-2](#) (core phase) and [Table 7-3](#) (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 7.1.5](#) for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5 Population

5.1 Patient population

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

5.2 Inclusion criteria

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

1. Written informed consent must be obtained prior to any screening procedures
2. Male and female patients ≥ 18 years of age
3. Patients with confirmed diagnosis of inadequately controlled acromegaly as evidenced by the following:
 - A mean GH concentration of a 5-point profile over a 2-hour period $\geq 1 \mu\text{g/L}$ and sex- and age-adjusted IGF-1 $>1.3 \times \text{ULN}$
4. Patients treated with high dose of octreotide LAR (30 mg or 40 mg) or lanreotide ATG (120 mg) given as monotherapy for at least 3 months prior to screening (Visit 1)
 - Note: Patients currently being treated with octreotide LAR 30 mg from countries where the octreotide LAR 40 mg dose is approved at the time of screening will start a run-in phase in which they will receive the 3 injections of octreotide LAR 40 mg before being evaluated for eligibility for the core phase of the study

5.3 Exclusion criteria

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

1. Concomitant treatment with other medications known to reduce GH and or IGF-1, other than octreotide LAR or lanreotide ATG, unless discontinued 3 months prior to visit 1 (screening)
2. Patients with compression of the optic chiasm causing any visual field defect that requires surgical intervention
3. Diabetic patients with poor glycaemic control as evidenced by HbA1c $>8\%$ at Visit 1 for Group 2 and at both Visit 1 and Visit 5 for Group 1
4. Patients who are hypothyroid and not on adequate replacement therapy
5. Patients with symptomatic cholelithiasis and acute or chronic pancreatitis
6. Patients with clinically significant valvular disease
7. Patients with risk factors for torsade de pointes, i.e. patients with a baseline QTcF >450 ms in males, and >460 ms in females
8. Hypokalaemia, hypomagnesaemia, uncontrolled hypothyroidism, family history of long QT syndrome or concomitant medications with known risk of Torsades de pointes (TdP). Drugs with possible risk of TdP should be avoided whenever feasible.
9. Patients who have congestive heart failure (NYHA Class III or IV), unstable angina, sustained ventricular tachycardia, clinically significant bradycardia, advanced heart block, history of acute MI less than one year prior to study entry or clinically significant impairment in cardiovascular function

10. Concomitant disease(s) that could prolong the QT interval such as autonomic neuropathy (caused by diabetes or Parkinson's disease), HIV, cirrhosis, uncontrolled hypothyroidism or cardiac failure
11. Patients with liver disease such as cirrhosis, chronic active hepatitis, or chronic persistent hepatitis, or patients with ALT/AST > 2.0 X ULN, serum bilirubin >2.0 X ULN
12. Presence of Hepatitis B surface antigen (HbsAg) or Hepatitis C antibody test (anti-HCV)
13. Patients with serum creatinine >2.0 X ULN
14. Patients with WBC <3 X 10⁹/L; Hb 90% < LLN; PLT <100 X 10⁹/L
15. Patients with the presence of active or suspected acute or chronic uncontrolled infection
16. Patients who have undergone major surgery/surgical therapy for any cause within 4 weeks prior to visit 1 (screening)
17. Patients with active malignant disease within the last five years (with the exception of basal cell carcinoma or carcinoma in situ of the cervix)
18. 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)
19. History of syncope or family history of idiopathic sudden death
20. History of immunocompromise, including a positive HIV test result (ELISA and Western blot). A HIV test will not be required; however, previous medical history will be reviewed
21. Known hypersensitivity to somatostatin analogues or any other component of the pasireotide LAR
22. Patients who have a history of alcohol or drug abuse in the 6 month period prior to receiving pasireotide
23. Patients who have given a blood donation (of 400 ml or more) within 2 months before receiving pasireotide
24. Patients who have participated in any clinical investigation with an investigational drug within 1 month prior to dosing
25. Patients with any current or prior medical condition that, in the judgment of the investigator may interfere with the conduct of the study or the evaluation of the study results
26. 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
27. Sexually active males unless they use a condom during intercourse while taking drug and for 3 months following last dose of pasireotide 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.
28. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test
29. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and 3 months following last dose of pasireotide. Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception)
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 months prior to screening). For female subjects on the study the vasectomized male partner should be the sole partner for that subject
- Combination of any two of the following (a+b or a+c, or b+c):
 - a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
 - b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
 - c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

6 Treatment

6.1 Study treatment

Pasireotide LAR 40 mg or 60 mg will be administered as intra-muscular (i.m.) injections every 4 weeks for the core and the extension phases of the study. Patients will begin their treatment with pasireotide LAR 40mg every 4 weeks. Dose down-titrations are permitted for patients who do not tolerate the protocol-specified dosing schedule. These dose adjustments are permitted in order to allow the patient to continue the study treatment. If tolerability issues occur, the dose is permitted to decrease by 20 mg. Please refer to [Section 6.2.1](#) for further instructions of dose adjustments. Octreotide LAR 40mg will be administered as intra-muscular injections every 4 weeks for the run-in phase if it applies. Dose up-titration of pasireotide LAR to 60mg will be allowed after 12weeks of treatment (i.e. after 3 injections) in patients who do not achieve adequate biochemical control and the 40mg is well tolerated. Prior to dose escalation it is recommended that glucose homeostasis is adequately controlled and that patients with HbA1c >8% should not have the dose of the pasireotide LAR increased to 60 mg.

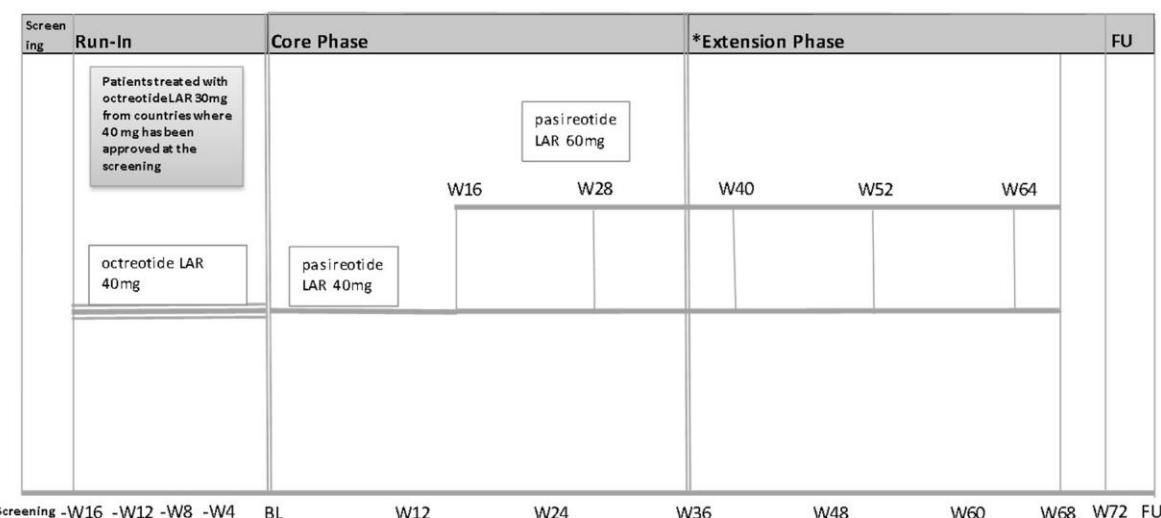
6.1.1 Dosing regimen

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
pasireotide	intra-muscular	20mg, 40mg, 60 mg	every 4 weeks
octreotide	intra-muscular	40mg	every 4 weeks

Group 1 – Dosing Regimen

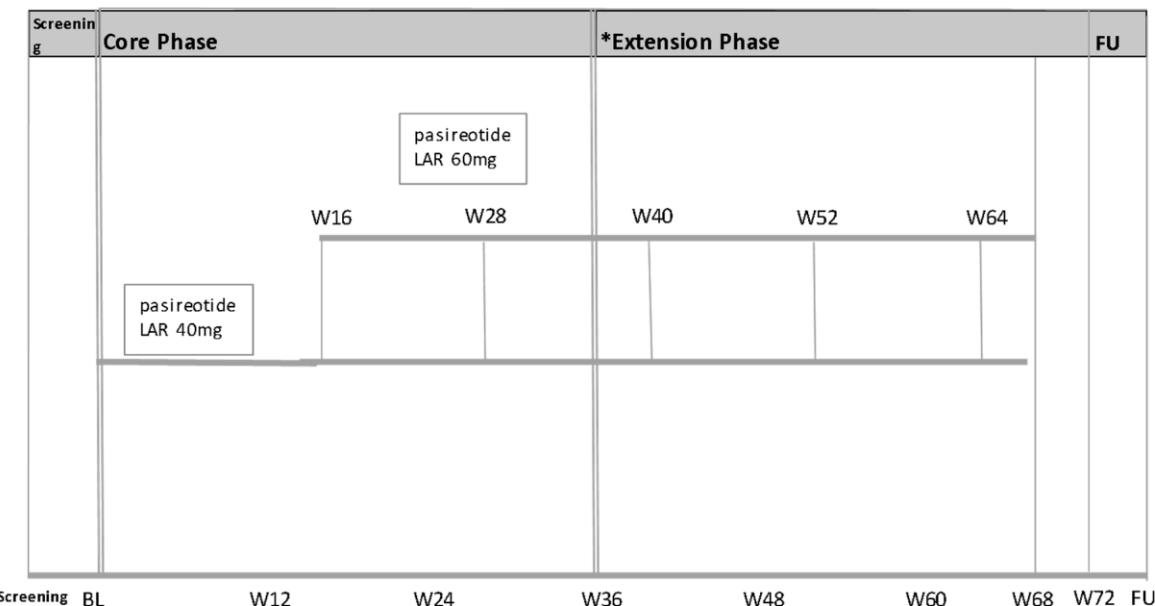
Figure 6-1 Group 1: Dose Regimen



* Patients who do not achieve biochemical control at the end of the core phase (or at any time during the extension phase) will be allowed to use concomitant medications used to treat acromegaly based on the investigator's clinical judgment.

Group 2 – Dosing Regimen

Figure 6-2 Group 2: Dose Regimen



* Patients who do not achieve biochemical control at the end of the core phase (or at any time during the extension phase) will be allowed to use concomitant medications used to treat acromegaly based on the investigator's clinical judgment.

6.1.2 Ancillary treatments

Not applicable.

6.1.3 **Rescue medication**

Not applicable.

6.1.4 Guidelines for continuation of treatment

For guidelines for continuation of treatment, refer to [Section 6.2 Dosing modification](#).

6.1.5 Treatment duration

Run-in Phase (Group 1 only)

Patients in this group will receive octreotide LAR 40 mg for 16 weeks in total. After the third injection, biochemical control will be assessed for the eligibility criteria.

Core phase

Patients will continue to receive pasireotide LAR 40 mg or 60 mg until week 36, when all assessments will be done(=Visit 18), receiving the last injection for the core phase at week 32 (=Visit17).

Extension phase

At the end of the core phase, patients will have the option to continue study treatment with pasireotide LAR until week 68 (=Visit 26). Patients who are not biochemically controlled during the extension will be allowed to receive concomitant treatment with medications used to treat acromegaly.

Patients can continue with study treatment until pasireotide LAR is commercially available and reimbursed in their respective country or until 68 weeks whichever occurs first. If pasireotide LAR is not commercially available and reimbursed and the patient is still receiving clinical benefit at 68 weeks as assessed by the investigator, the patient will have the opportunity to receive pasireotide LAR via a roll over study or a local access program if available.

6.1.6 Dose escalation guidelines

Not applicable.

6.2 Dose modifications

6.2.1 Dose modification and dose delay

Patients will begin their treatment with pasireotide LAR 40 mg every 4 weeks. Dose up-titration of pasireotide LAR to 60 mg will be allowed after 12 weeks of treatment (i.e. after 3 injections) in patients who do not achieve adequate biochemical control and the 40 mg is well tolerated. Prior to dose escalation it is recommended that glucose homeostasis is adequately controlled and that patients with HbA1c >8% should not have the dose of the pasireotide LAR increased to 60 mg.

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. If tolerability issues occur, the dose is permitted to decrease by 20 mg. Once the tolerability issue resolves, the dose should be returned to the one prior to the dose reduction. For guidance refer to [Table 6-2](#).

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

LAR treatment	Adverse event	Action
Pasireotide LAR i.m.	AE CTC grade \leq 2 AE CTC grade \geq 3 and assessed as study drug related	No drug adjustments Reduce pasireotide LAR i.m. dose by 20 mg If the AE improves to grade \leq 2 before the next administration, increase dose back to the prior dose. If the dose is increased and the AE recurs at a grade \geq 3, the dose should be reduced again. The patient should stay on this lower dose if clinical benefits are maintained. No further dose titrations are allowed. If the AE does not improve to grade \leq 2, the dose is to be reduced further if clinical benefits are maintained. If the AE does not improve to grade \leq 2 on the minimum study dose, the treatment should be stopped. The patient should be discontinued and followed up for safety.

For the management of hyperglycemia, QT prolongation and LFT increases refer to specific instructions provided in [Section 6.2.2.3](#), [Section 6.2.2.1](#), and [Section 6.2.2.2](#).

In case of over-efficacy (i.e. IGF-1 levels below the LLN), the dose can be reduced based on the investigator's judgment.

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

6.2.2 Follow-up for toxicities

6.2.2.1 QT-prolongation

The results of the ECGs, cardiac examination and any recommendation provided by the cardiologist must be evaluated by the investigator to determine whether the patient should continue in the trial or not (discontinuation criteria to be followed).

6.2.2.1.1 $480 \text{ msec} < \text{QTcF} \leq 500 \text{ msec}$

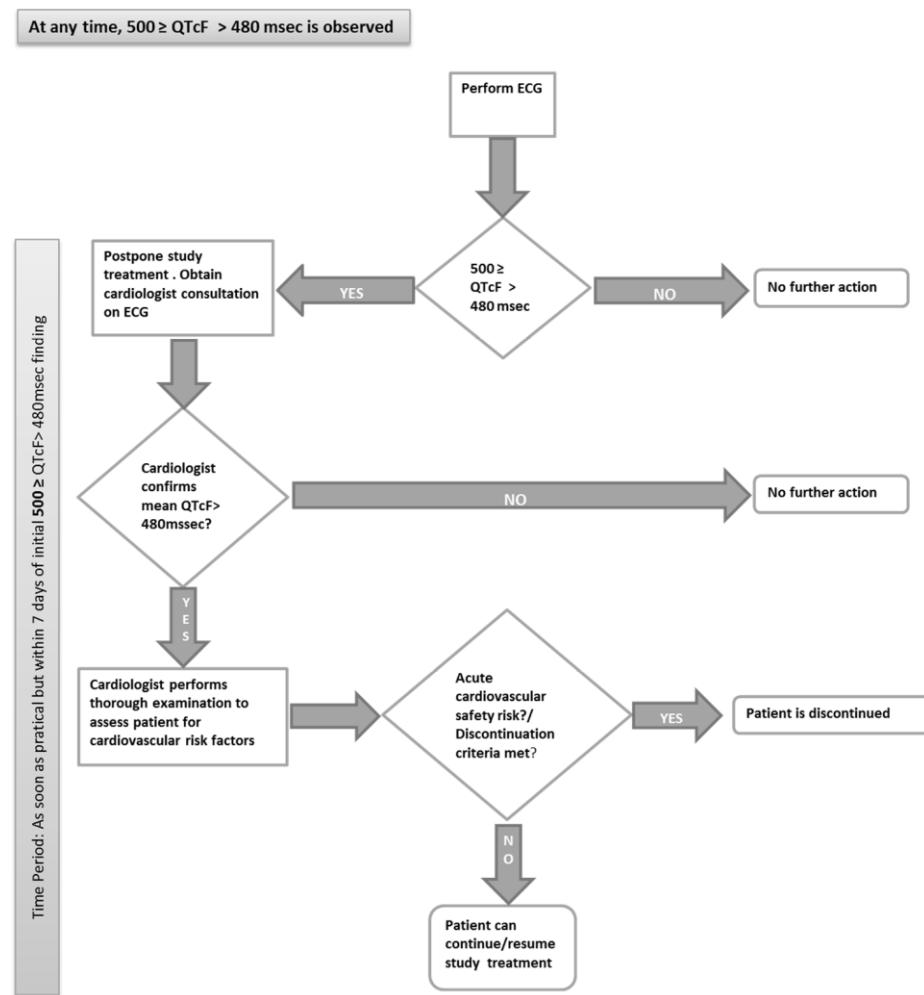
If at any visit a $480 \text{ msec} < \text{QTcF} \leq 500 \text{ msec}$ is observed for a first time for a patient at a given dose level, the following steps need to be taken (refer to [Figure 6-3](#)):

A cardiology consultation must be sought as soon as practical but within 7 days of the initial finding of abnormal ECG and the cardiologist must re-evaluate the ECG. The study treatment will be postponed until a cardiologist has re-evaluated the ECG.

- If a $\text{QTcF} > 480 \text{ msec}$ is NOT confirmed, no further action needs to be taken.
- If a $\text{QTcF} > 480 \text{ msec}$ is confirmed, a cardiologist must perform a thorough examination (such as reviewing baseline ECG, concurrent medications and performing a cardiovascular examination, including at least a cardiac auscultation) to assess the patient for cardiovascular risk factors.
 - If based upon the assessment by the cardiologist, the investigator considers that there is an acute cardiovascular safety risk and that the patient should not continue with study medication, the patient needs to be discontinued immediately (discontinuation criteria to be followed).

- If following the examination by the cardiologist, the investigator considers that there is no acute cardiovascular safety risk the patient could continue to receive study medication.

Figure 6-3 QT prolongation flowchart: 480 msec less than QTcF less than or equal to 500 msec



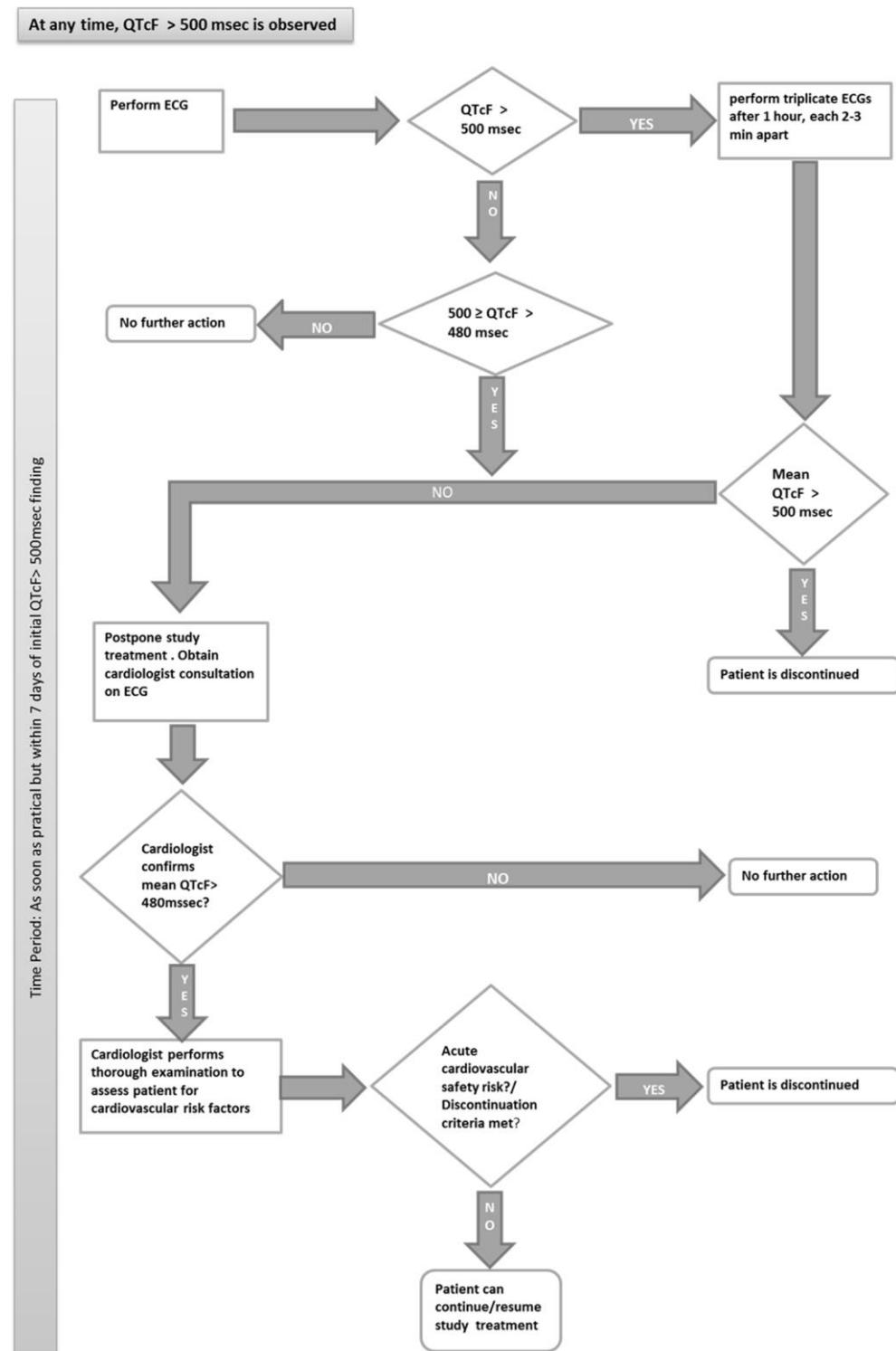
6.2.2.1.2 QTcF > 500msec

If at any visit a QTcF > 500msec is observed, the following steps need to be taken (refer to [Figure 6-4](#)):

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 > 500msec, the patient has to postpone study treatment until a cardiologist has re-evaluated the ECG. The re-evaluation needs to be done as soon as practical but within 7 days of the initial finding of abnormal ECG.

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

Figure 6-4 QT prolongation flowchart; QTcF greater than 500msec



6.2.2.2 Hepatic Safety management

Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding. If the finding is confirmed, the patient should be followed with frequent liver function monitoring until values return to pre-treatment levels.

If any of the criteria below are observed at any scheduled or unscheduled visit the sponsor should be notified immediately upon awareness and the hepatic safety follow up should be performed within **72 hours** of awareness of the abnormality:

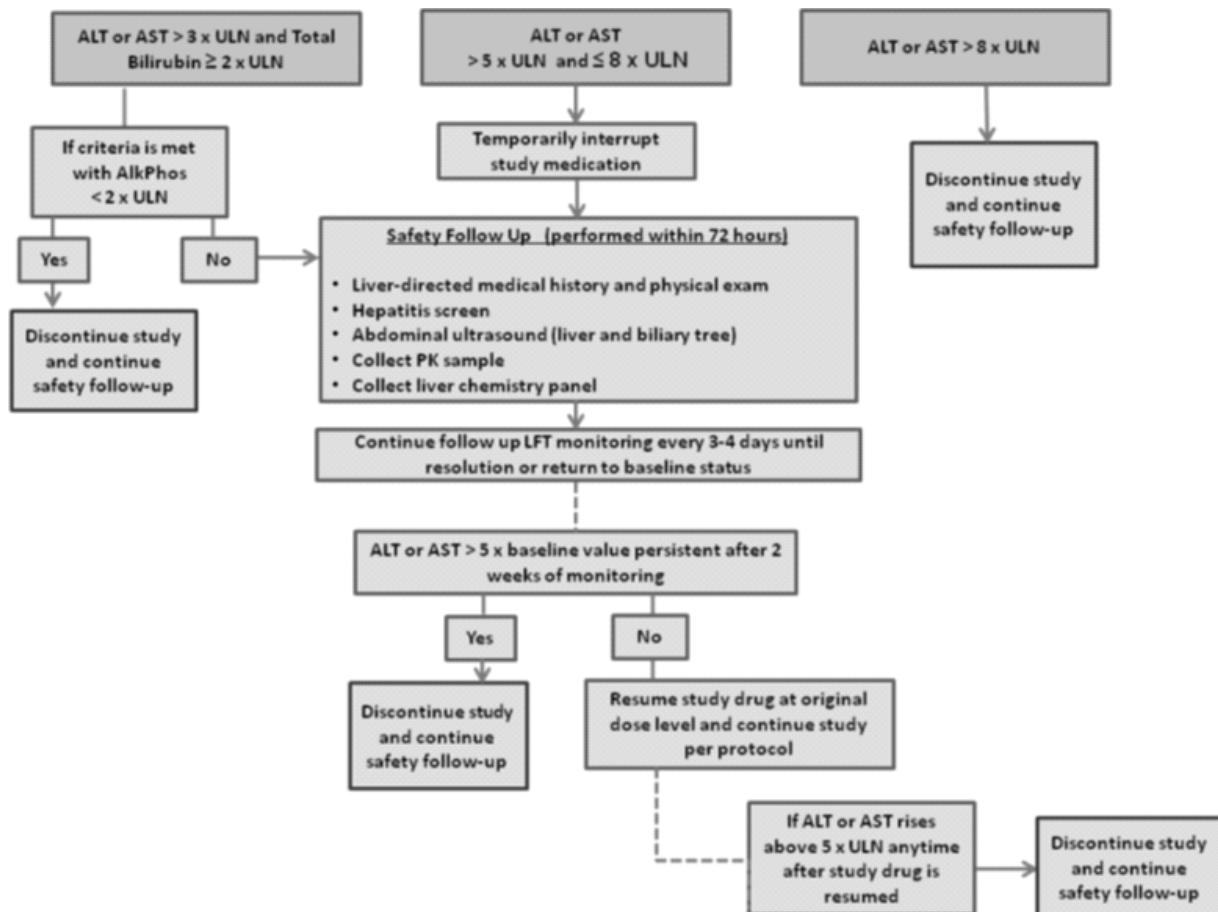
- ALT or AST $> 3 \times$ ULN and Total Bilirubin $\geq 2 \times$ ULN
- ALT or AST $> 5 \times$ ULN and $\leq 8 \times$ ULN
- ALT or AST $> 8 \times$ ULN

Hepatic Safety Follow up:

- Perform liver-directed medical history and physical examination (i.e. assess occupational hazards, concomitant medications including over-the-counter medications, inter-current illness, etc.)
- Liver chemistry tests: ALT, AST, total bilirubin, (fractionate to direct/indirect bilirubin if total bilirubin is $> 2.0 \times$ ULN), Albumin, PT (INR), ALP, and GGT. These tests should be monitored every **3-4 days** until resolution or return to baseline status.
- 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)

Patients should be managed according to the LFT algorithm [Figure 6-5](#) Patients may need to be discontinued if the abnormal liver function criteria are met upon LFT retesting or immediately discontinued without LFT retesting in the case of ALT or AST > 8 times the upper limit of normal (see discontinuation criteria [Section 7.1.5.1](#)). Progress reports of the event should be maintained until resolution or return to baseline status.

If any of these criteria are met and deemed an AE by the investigator, the event must be recorded on the Adverse Event CRF page; if the event is deemed serious by the investigator, then the SAE form should be completed. In addition, any clinically significant findings from the physical examination should be recorded on the Adverse Event CRF page.

Figure 6-5 LFT management algorithm

6.2.2.3 Hyperglycemia

Hyperglycemia is known to be associated with the treatment of somatostatin analogues (SSA). Clinical studies of pasireotide in healthy volunteers and in patients with Cushing's disease, acromegaly or carcinoid syndrome have reported transient, asymptomatic increases in fasting and postprandial glucose levels. Two clinical studies have been conducted [SOM230B2216] and [SOM230B2124] in healthy volunteers to further understand the mechanism of pasireotide-induced hyperglycemia and to evaluate the potential clinical utility of anti-diabetes agents in the management of pasireotide-induced hyperglycemia. Data from [SOM230B2216] study indicate that pasireotide decreases insulin secretion, particularly in the postprandial period, as well as the GLP-1/GIP secretion. Results from [SOM230B2124] study suggest that the incretin-based therapies (GLP-1 analogues and DPP-4 inhibitors) may have the best potential to manage the hyperglycemia associated with pasireotide. Some patients in [SOM230B2305], [SOM230C2305] and the [SOM230C2402] trials required insulin to treat their hyperglycemia.

Prior to dose escalation it is recommended that glucose homeostasis is adequately controlled and that patients with HbA1c >8% should not have the dose of the pasireotide LAR increased to 60 mg.

6.2.2.3.1 Self-monitoring of blood glucose

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

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

In addition to self-monitoring, fasting plasma glucose and HbA1c will be collected at study visits per [Table 7-1](#) to [Table 7-3](#). Close and frequent monitoring of blood glucose is needed during pasireotide treatment. Intervention for hyperglycemia is to be implemented in any patient meeting any of the following criteria: $FPG > 130\text{mg/dL}$ or $\text{HbA1c} \geq 6.5\%$.

Patients with $FPG > 160\text{mg/dL}$ or $\text{HbA1c} > 7.5\%$ 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 $> 250\text{mg/dL}$; $> 13.9\text{ mmol/L}$) at any point in the study should have the dose of pasireotide decreased. Patients who in spite of appropriate therapeutic interventions and despite dose reduction of study drug develop uncontrolled diabetes mellitus and/or consistently high blood glucose values: $FPG \geq 240\text{mg/dL}$ (13.3 mmol/L) or HbA1c value $\geq 10\%$ will require study treatment discontinuation.

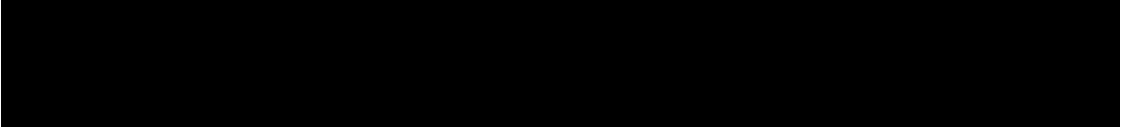
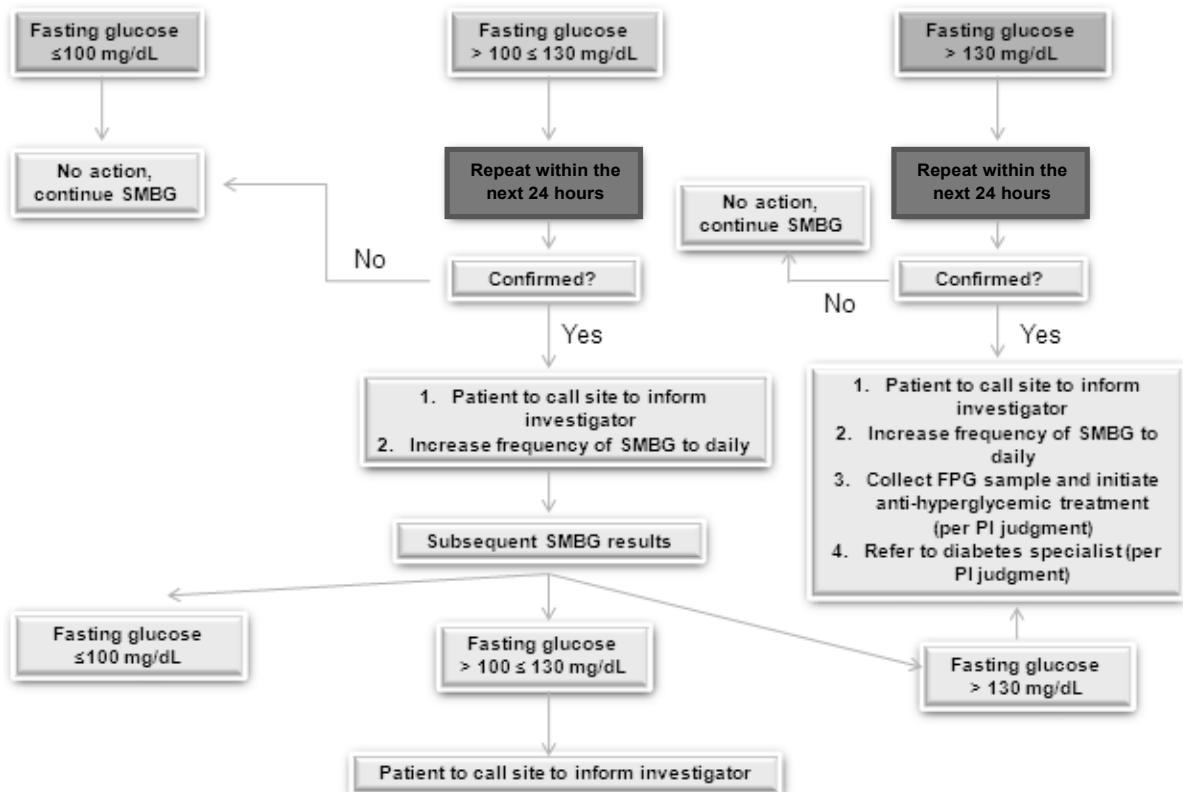


Figure 6-6 Fasting SMBG Guidance



6.2.3 Anticipated risks and safety concerns of the study drug

Appropriate eligibility criteria, as well as specific dose modification and stopping rules are included in this protocol. Refer to [Section 7.1.5](#) for details.

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 increases are provided in [Section 6.2.2](#). Refer to preclinical toxicity and or clinical data found in the current [Investigator's Brochure].

6.3 Concomitant medications

6.3.1 Permitted concomitant therapy

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Concomitant Medications and Significant Non-Drug Therapies CRF. Diabetic patients must continue their treatment for diabetes throughout the study as indicated. If oral contraception is used, the patient must have been practicing this method of birth control for at least three months prior to enrollment and must agree to continue the oral contraceptive throughout the course of the study and for 12 weeks after the last dose of study drug.

6.3.1.1 Permitted concomitant therapy requiring caution and/or action

Acromegaly concomitant therapy is allowed only during the extension period for patients who do not achieve biochemical control.

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

6.3.2 Prohibited concomitant therapy

The use of concomitant medication with a known risk of TdP is prohibited. In case a patient needs to take medication with a known risk of TdP, it will require study drug discontinuation prior to starting the medication. Please see [Appendix 3](#) for further guidance on medication with a known risk to TdP.

The following washouts are to be followed prior to screening

1. Dopamine agonists (bromocriptine, cabergoline) or pegvisomant (INN); 12 weeks
2. Pasireotide s.c.: 12 weeks
3. Pasireotide LAR: 12 weeks

6.4 Patient numbering, treatment assignment or randomization

6.4.1 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 Subject Number (Subject No.) consists of the Center Number (Center No.) (As assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form the patient is assigned to the next sequential Subject No. available to the investigator.

The investigator or designated staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. Once assigned, the Subject No. must not be reused for any other subject and the Subject No. for that individual must not be changed, even if the patient is re-screened. If the patient fails to be randomized or start treatment for any reason, the reason will be entered into the Screening Log. IRT must be notified within 2 days that the patient was not enrolled.

6.4.2 Treatment assignment or randomization

Prior to dosing, all patients who fulfill all inclusion/exclusion criteria will be assigned to pasireotide LAR 40 mg treatment arm. The investigator or his/her delegate will call or log on to the IRT and confirm that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a patient number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number but only for the pasireotide LAR treatment.

6.4.3 Treatment blinding

Not applicable.



6.5 Study drug preparation and dispensation

Detailed instructions on the use of pasireotide LAR for i.m. injection and octreotide LAR 40mg are provided in the pharmacy manual.

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug(s) will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

Pasireotide LAR will be provided as microparticles powder in vials containing nominally 20, 40 and 60 mg of Pasireotide (as free base) and solvent for suspension for injection in ampules for the reconstitution of the LAR microparticles.

Octreotide LAR 40 mg will be locally supplied to the site.

6.5.1 Study drug packaging and labeling

The study medication packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the treatment arms and a [specific visit or dose/dose level]. Responsible site personnel will identify the study treatment package(s) to dispense to the patient by using the IRT and obtaining the medication number(s). Site personnel will add the patient number on the label. Immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique patient number.

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

Table 6-3 Packaging and labeling

Study treatments	Packaging	Labeling (and dosing frequency)
Pasireotide LAR	Microparticle powder for suspension in vial Solution for suspension (vehicle) in ampoule or pre-filled syringe	Labeled as 'SOM230' LAR (once/28days) Labeled as 'SOM230 Solvent' (once/28days)
Octreotide LAR	Octreotide LAR sourced locally	Octreotide LAR sourced locally

6.5.2 Drug supply and storage

Study drugs must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the study drugs should be stored according to the instructions specified on the drug labels and in the current [Investigator's Brochure].

Table 6-4 Supply and storage of study treatments

Study treatments	Supply	Storage
Pasireotide LAR	Centrally or locally supplied by Novartis	Refer to study treatment label
Octreotide LAR	Octreotide LAR sourced locally	Refer to the label

6.5.3 Study drug compliance and accountability

6.5.3.1 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.

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

6.5.3.2 Study drug accountability

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

At study close-out, and, as appropriate during the course of the study, the investigator will return all 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.

6.5.3.3 Handling of other study treatment

Not applicable.

6.5.4 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 to Table 7-3 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. No CRF except Quality of Life Questionnaire will be used as a source document.

For all dosing visits, there is a general \pm 2 day window on assessments to take into account scheduling over public holidays. For all safety visits (visit without dosing), there is a general \pm 1 day window on assessments to take into account scheduling over public holidays.

Patients who discontinue treatment early must perform an end of core/extension phase visit 28 \pm 2 days from the last dose.

Table 7-1 Core Phase Visit evaluation schedule – Group 1

Table 7-2 Core Phase Visit evaluation schedule – Group 2

Table 7-3 Extension Phase Visit evaluation schedule for both Group 1 and Group 2

	Category	Protocol Section											Extension phase completion / discontinuation	Safety Follow Up	Study Evaluation Completion
Visit Number			18	19	20	21	22	23	24	25	26	778		779	
Study Week			36	40	44	48	52	56	60	64	68		8 weeks after last study drug administration		
IRT Registration	D	7.1.2	x	x	x	x	x	x	x	x	x				
Patient history															
concomitant medications	D	7.1.2.3		x	x	x	x	x	x	x	x	x	x		
Physical examination	S	7.2.2.1				x			x			x			
Height	D	7.2.2.3										x			
Weight	D	7.2.2.3				x			x			x			
Vital signs	D	7.2.2.2		x	x	x	x	x	x	x	x	x			
Symptoms of acromegaly	D	7.2.1.2.3		x	x	x	x	x	x	x	x	x			
Laboratory assessments															
Hematology	D	7.2.2.4.1				x			x			x			
Clinical Chemistry (except LFT)	D	7.2.2.4.2				x			x			x			
LFT (ALT, AST, T-bil, Alb, ALP, γ -GT)	D	7.2.2.4.3				x			x			x			
Coagulation (APTT, PTT and PT(INR))	D	7.2.2.4.5				x			x			x			
5-point GH and IGF-1	D	7.2.1.1.1/7.2.1.1.2				x			x			x			
Fasting blood glucose	D	7.2.2.4.6		x	x	x	x	x	x	x	x	x			
HbA1c	D	7.2.2.4.6			x			x				x			
oGTT	D	7.2.2.4.6										x			

7.1.1 Molecular pre-screening

Not applicable

7.1.2 Screening

The informed consent must be signed prior to ANY screening procedure being performed. The site should enter the IRT when a patient signs the informed consent and begins his/her screening. Patients that do not meet eligibility criteria are allowed to be rescreened and should use the same patient number. Rescreening should be documented in the source files. Should the cause of screening failure be normal GH and/or IGF-1, patients can be rescreened once these parameters go beyond the control level, provided that at least a 3-month treatment with maximal doses of first generation SSAs has been given to the patient.

7.1.2.1 Eligibility screening

Following registration in the IRT for screening, patient eligibility will be checked once all screening procedures are completed. For Group 1 patients, patient eligibility will be checked again at the end of the run-in period prior to the baseline. The eligibility check will be embedded in the IRT system. Please refer and comply with detailed guidelines in the IRT Manual.

7.1.2.2 Information to be collected on screening failures

Patients who sign the informed consent, but fail to be started on study treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the applicable Screening Failure CRF pages. If the patient fails to be enrolled, the IRT must be notified within 2 days of the screen fail that the patient was not enrolled.

7.1.2.3 Patient demographics and other baseline characteristics

Standard demographic information and medical history will be collected. History of acromegaly, prior medications for acromegaly, AIP mutation and information on MRIs performed as standard of care will also be collected. Other baseline assessments will be collected as per [Table 7-1](#) and [Table 7-2](#).

7.1.3 Run-in period

If a patient is considered as a Group 1, the run-in phase is required. Patients will be treated with octreotide LAR 40 mg for 16 weeks. The eligibility will be re-assessed after 3 injections of octreotide LAR 40 mg.

7.1.4 Treatment period

Core Phase

Patients will be treated with pasireotide LAR until week 36, receiving the last core injection at week 32, unless they discontinue from the study treatment due to any reason. The core phase completion visit is required at week 36. The safety follow up assessment is also required 56 days after the last study drug administration.

For details of assessments refer to [Table 7-1](#) and [Table 7-2](#).

Extension Phase

Patients will be treated with pasireotide LAR until 68 weeks, unless they discontinue from the study treatment due to any reason. Starting from week 40, acromegaly concomitant therapy is allowed for patients who do not achieve the biomedical control. The extension phase completion visit is required at week 72. The safety follow up assessment is also required 56 days after the last study drug administration.

For details of assessments refer to [Table 7-3](#).

7.1.5 End of treatment visit including study completion and premature withdrawal

Patients who discontinue study treatment before visit 777 (week 36) in the core phase and visit 778 (week 72) in the extension phase, should be scheduled for a visit as soon as possible to have all assessments listed for the 777 or 778 visits performed ([Table 7-1](#) to [Table 7-3](#)). A Study Completion CRF page should be completed, giving the date and reason for stopping the study treatment. At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 56 days following the last dose of study treatment.

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

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

The investigator must contact IRT to register the patient's discontinuation.

For criteria for premature withdrawal refer to [Section 7.1.5.1](#).

7.1.5.1 Criteria for premature patient withdrawal

Patients may voluntarily withdraw from the study or be discontinued 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 values (s) and abnormal test procedures results (s)
- Patient withdrew consent
- Protocol deviation
- Physician decision
- Administrative problems

Patients must be withdrawn from the study in case of:

- Pregnancy
- Lost to follow up
- Death

In addition to the general withdrawal criteria, the study specific criteria below also require immediate study drug discontinuation. The safety follow-up management should be performed as outlined in [Section 6.2.2](#). Re-challenge of study medication is prohibited once discontinuation criteria are met.

Hepatic-related discontinuation criteria

- Jaundice or other signs of clinically significant liver dysfunction
- ALT or AST $> 3 \times$ ULN and Total Bilirubin $\geq 2 \times$ ULN and ALP $< 2 \times$ ULN
- ALT or AST $> 5 \times$ ULN $\leq 8 \times$ ULN persistent for more than 2 weeks
- ALT or AST $> 8 \times$ ULN

QT related discontinuation criteria

Patients experiencing adverse events in QTc:

- QTcF > 500 msec, if confirmed by a cardiologist.
- QTcF > 480 msec, if the investigator determines it is no longer safe for the patient to continue in the study, based on ECGs, cardiac examination and recommendation from a cardiologist.
- Clinically significant arrhythmias including:
 - Any ventricular or supra-ventricular tachyarrhythmia associated with symptoms of hemodynamic compromise.
 - Sustained ventricular tachycardia (>30 s) irrespective of symptoms.
 - Clinically significant brady-arrhythmia or third degree AV block.
- Need to use QT prolonging medication with known risks factors for torsade de pointes.

Hyperglycemia related discontinuation criteria

- Uncontrolled diabetes mellitus (DM), consistently high capillary glucose values in excess of 275 mg/dL (15.5 mmol/L), FPG \geq 240 mg/dL (13.3 mmol/L) or HbA1c value \geq 10 % despite prior appropriate management and prior dose adjustment of the study drug

The investigator must also notify the IRT of the premature withdrawal, if this occurs during the core period. Patients who withdraw prematurely from the core phase cannot participate in the extension phase.

7.1.6 Follow-up and End of Study visit

All patients must have safety evaluations and complete the safety follow up assessments at the 56 days after the last dose of pasireotide LAR.

Patients lost to follow up should be recorded as such on the CRF. For patients who are lost to follow-up, the investigator should show “due diligence” by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. Patients that meet the requirements for follow up of abnormal LFTs at the end of study visit should be followed up as detailed in [Section 6.2.2.2](#).

7.2 Assessment types**7.2.1 Efficacy assessments****7.2.1.1 GH (5-point mean GH level)**

A 5-point mean GH will be assessed from a 2-hour profile after one hour at rest at the hospital and prior to the study drug administration at week -20 (Group1 only), week -4, week 12, 24, 36 in the core phase and at week 48, 60, 72 in the extension phase.

The 5-point mean GH profile is to be done within a 2-hour time period prior to glucose intake when an oGTT is required.

All GH 2-hour profiles should be taken at the same time in the morning. The samples for GH will be analyzed by the central laboratory. Please refer to the central laboratory's [\[Clinical Trial Laboratory Manual\]](#) for processing details.

7.2.1.1.2 IGF-1

Total IGF-1 levels will be assessed at the same visits as GH with one pre-dose sample which is week -20 (Group1 only), week -4, week 12, 24, 36 in the core phase and at week 48, 60, 72 in the extension phase. Blood sampling for IGF-1 will be done prior to the study drug administration and glucose intake for oGTT when applicable. This sample must be taken together with the first sample of the GH profile. The samples for IGF-1 will be analyzed by the central laboratory. Please refer to the laboratory's [\[Clinical Trial Laboratory Manual\]](#) for processing details.

7.2.1.2 Secondary efficacy assessments

7.2.1.2.1 GH and IGF-1:

Both values in combination or alone will be used to assess secondary efficacy parameters at week 12, 24 and 36 in the core phase and at week 48, 60 and 72 in the extension phase.

7.2.1.2.2 Health-Related Quality of Life (HRQoL)

Patient Reported Outcomes Assessment:

HRQoL will be assessed at baseline, week 12, 24, visit 777(core phase completion) and at visit 778 (extension phase completion) using the AcroQoL, an acromegaly-specific quality of life instrument. The AcroQoL instrument is comprised of 22 questions divided into two scales: one evaluating physical aspects (8 items) and the other that addresses psychological aspects (14 items). The psychological scale can also be further divided into subscale that evaluates physical appearance and the other subscale focused on the impact of the disease on personal relationships of the patient (7 items each). Each of the questions has a 5-item Likert scale. The instrument was developed with input from both physicians and patients to assess those dimensions of health-related quality of life most relevant and bothersome to patients with this disease. It has been found to be a valid, reliable instrument, that is sensitive to changes in the concepts being measured ([Badia et al 2004](#)).

Health Status:

Health status will be measured at baseline and weeks 12, 24, visit 777 and visit 778 using the EQ-5D-5L, a valid and reliable instrument for measuring general health status. The EQ-5D-5L consists of 2 pages – the descriptive system and the EQ visual analogue scale (EQ VAS) ([Herdman M et al 2011](#)) The descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each with 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ VAS records the respondent's self-rated health on a 20 cm vertical, visual analogue scale with endpoints labeled 'the best health you can imagine' and 'the worst health you can imagine'

Laboratory evaluations.

7.2.1.2.3 Symptoms of acromegaly

Symptom of acromegaly are to be collected at visits indicated in [Table 7-1](#) to [Table 7-3](#) and appropriate CRFs. Ring size will be measured with a gauge using 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 measurement will be provided on a scale of 1-15 including half sizes. The investigator will also ask the patient to score the following symptoms of acromegaly: headache, fatigue, perspiration, paresthesias, osteoarthralgia according to a five-point score scale (0=absent, 1=mild, 2=moderate, 3=severe, 4=very severe).

7.2.2 Safety and tolerability assessments

7.2.2.1 Physical examination

A complete physical examination must be performed by the investigator at visits indicated in [Table 7-1](#) to [Table 7-3](#). The examinations will be performed according to the standards at each institution.

Information about the physical examination must be present 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 Medical History/Current Medical Condition page on the patient's CRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's CRF.

7.2.2.2 Vital signs

Vital signs (supine blood pressure, supine pulse rate and body temperature) will be performed by the investigator at all visits as indicated in [Table 7-1](#) to [Table 7-3](#) and appropriate CRFs.

7.2.2.3 Height and weight

Height in centimeters and weight to the nearest 0.1 kilogram (in indoor clothing, but without shoes) are to be collected at visits indicated in [Table 7-1](#) to [Table 7-3](#) and appropriate CRFs.

7.2.2.4 Laboratory evaluations

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

Urinalysis and urine pregnancy test will be performed by dipstick locally. The dipsticks will be provided to the sites by the central laboratory.

Table 7-4 Local or Central Clinical Laboratory Parameters Collection Plan

Test Category	Test Name
Hematology (central)	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, RBC Morphology with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)
Clinical Chemistry (central)	Bicarbonate, Calcium, Chloride, Creatinine, Creatine Kinase, Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, α -amylase, Lipase, Lactic Dehydrogenase (LDH), Magnesium, Sodium, Potassium, Prolactin,
LFT (central)	ALT, AST, Total bilirubin, (total bilirubin should be differentiated into direct and indirect reacting bilirubin if total bilirubin is increased > 2.0 ULN), Albumin, ALP and GGT
Hepatic Screening (central)	HbsAg, AntiHCV
Hyperglycemia related test (central)	Fasting Blood Glucose, Glycosylated Hemoglobin (HbA1C), oGTT (insulin and plasma glucose)
Coagulation (central)	Prothrombin time (PT) or International normalized ratio (INR), Partial thromboplastin time (PTT), Activated partial thromboplastin time (APTT)

Test Category	Test Name
Thyroid and hormones (central)	T4 [free], TSH, Plasma Adrenocorticotropic Hormone (ACTH), Fasting Serum Cortisol,
Urinalysis (local)	Macroscopic Panel (Dipstick) (Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, pH, Protein, Specific Gravity)
Additional tests (central)	Insulin-like growth factor 1 (IGF-1), Growth Hormone (GH)
Pregnancy Test	Urine (dipstick) and serum B-hCG

7.2.2.4.1 Hematology

Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, RBC Morphology with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils) are to be collected at visits indicated in [Table 7-1](#) to [Table 7-3](#).

7.2.2.4.2 Clinical Chemistry

Bicarbonate, Calcium, Chloride, Creatinine, Creatine Kinase, Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, α -amylase, Lipase, Lactic Dehydrogenase (LDH), Magnesium, Sodium, Potassium, Prolactin are to be collected at visits indicated in [Table 7-1](#) to [Table 7-3](#).

7.2.2.4.3 Liver function testing (LFT)

ALT, AST, Total bilirubin, (total bilirubin should be differentiated into direct and indirect reacting bilirubin if total bilirubin is increased > 2.0 ULN), Albumin, ALP and GGT are to be collected at visits indicated in [Table 7-1](#) to [Table 7-3](#).

7.2.2.4.4 Hepatic Screening

HbsAg, AntiHCV are to be collected at visit 1.

7.2.2.4.5 Coagulation

Prothrombin time (PT) or International normalized ratio (INR), Partial thromboplastin time (PTT), Activated partial thromboplastin time (APTT) are to be collected at visits indicated in [Table 7-1](#) to [Table 7-3](#).

7.2.2.4.6 Hyperglycemia related test

Fasting Blood Glucose, Glycosylated Hemoglobin (HbA1C), oGTT (insulin and plasma glucose) are to be collected at visits indicated in [Table 7-1](#) to [Table 7-3](#). Diabetic patients are not required to perform oGTT. If the patient discontinues from the study, the oGTT at visit 777/778 can be performed based on the judgment of the investigator.

7.2.2.4.7 Thyroid and hormones

T4 (free), TSH, ACTH, Fasting Serum Cortisol are to be collected at visits indicated in [Table 7-1](#) to [Table 7-3](#).

7.2.2.4.8 Urinalysis

Dipstick measurements for Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, pH, Protein, Specific Gravity are to be collected at visits indicated in [Table 7-1](#) to [Table 7-3](#).

7.2.2.4.9 Pregnancy

All pre-menopausal women who are not surgically sterile will have a serum B-hCG pregnancy test at screening, baseline and end of treatment (visit 777 and visit 778) and urine pregnancy test at visits indicated in [Table 7-1](#) to [Table 7-3](#)

A positive pregnancy test by urine is required an immediate serum B-hCG pregnancy test.

A positive pregnancy test requires immediate interruption of study treatment until the assessment is confirmed. If positive, the patient must discontinued from the study.

7.2.2.5 Gallbladder ultrasound

Table 7-5 Gallbladder Ultrasound Assessment Collection Plan

Group 1

Procedure	Screening/Run-in/Baseline	During Treatment/Follow-up
Gallbladder Ultrasound	Mandated (Week -20 and Week -4)	Week 12, 24, Visit 777 (core phase) Week 60, Visit 778 (extension phase)

Group 2

Procedure	Screening/Baseline	During Treatment/Follow-up
Gallbladder Ultrasound	Mandated (Week -4)	Week 12, 24, Visit 777(core phase) Week 60, Visit 778 (extension phase)

A gallbladder ultrasound will be performed at the sites at visits indicated in [Table 7-1](#) to [Table 7-3](#). The results will be recorded in the CRFs.

7.2.2.6 Cardiac assessments

7.2.2.6.1 Electrocardiogram (ECG)

Table 7-6 Central ECG Collection Plan

Group 1

Week	Time	ECG Type
-20 (Screening Run-In)	Pre-dose	12 Lead
-4 (Run-in)	Pre-dose	12 Lead
0 (Baseline)	Pre-dose	12 Lead
3	At any time during the visit	12 Lead
4	Pre-dose	12 Lead

Week	Time	ECG Type
7	At any time during the visit	12 Lead
8	Pre-dose	12 Lead
11	At any time during the visit	12 Lead
12	Pre-dose	12 Lead
Every 4 weeks until Visit 777 (core phase), until week Visit 778 (extension phase)	Pre-dose	12 Lead
Unscheduled visit	As clinically indicated	12 Lead

Group 2

Week	Time	ECG Type
-4 (Screening)	Pre-dose	12 Lead
0 (Baseline)	Pre-dose	12 Lead
3	At any time during the visit	12 Lead
4	Pre-dose	12 Lead
7	At any time during the visit	12 Lead
8	Pre-dose	12 Lead
11	At any time during the visit	12 Lead
12	Pre-dose	12 Lead
Every 4 weeks until Visit 777 (core phase), until Visit 778 (extension phase)	Pre-dose	12 Lead
Unscheduled visit	As clinically indicated	12 Lead

Standard 12 lead ECGs will be performed at the sites at visits indicated in [Table 7-1](#) to [Table 7-3](#).

If at any visit QTcF >480 msec is observed, all the procedures for QT-prolongation described in [Section 6.2.2.1](#) should be followed.

Interpretation of the tracing must be made by a qualified physician and documented on the ECG CRF page. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities present when the patient signed informed consent should be reported on the Medical History CRF. Clinically significant findings must be discussed with Novartis prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events CRF.

Each ECG should be taken prior to the study drug administration. At the discontinuation (including the core phase completion visit for patients who do not participate in the extension phase) or the extension phase completion visit, the ECG should be taken prior to the commercial drug administration.

7.2.2.6.2 Cardiac imaging - MUGA (multiple gated acquisition) scan or echocardiogram

Not applicable.

7.2.2.6.3 Cardiac enzymes

Not applicable.

7.2.2.7 Tolerability

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

7.2.3 Pharmacokinetics

Not applicable

7.2.3.1 Other assessments

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

7.2.4 Resource utilization

Not applicable

8 Safety monitoring and reporting

8.1 Adverse events

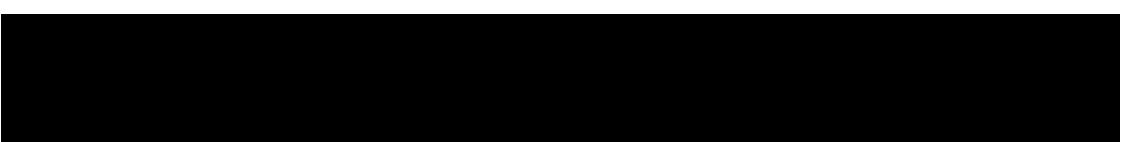
8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Except for screening failures, adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Relevant Medical History/Current Medical Conditions CRF. Adverse event monitoring should be continued for at least 8 weeks following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate adverse event.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.



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

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

1. The severity grade
2. Its duration
3. Its relationship to the study treatment
4. Action taken with respect to study or investigational treatment
5. Whether medication or therapy was given
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 CRF.

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

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

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

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

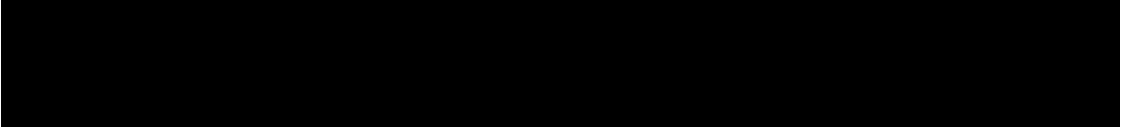
8.1.3 Adverse events of special interest

Adverse events of special interest including the following:

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

8.1.3.1 Definitions and reporting

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



8.2 Serious adverse events

8.2.1 Definitions

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

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

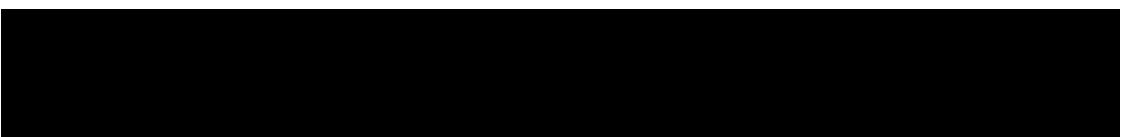
8.2.2 Reporting

To ensure patient safety every SAE regardless of suspected occurring after the patient has provided informed consent and until at least 8 weeks after the patient has stopped study drug administration must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 8 weeks 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 in English, and send the completed, signed form by fax within 24 hours to the oncology Novartis Drug Safety and Epidemiology (DS&E) department.

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



provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

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

Not applicable.

8.4 Pregnancies

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

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

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.

Newborn of a patient (or a partner of a patient) who becomes pregnant during the study treatment or within 3 months after the last pasireotide LAR dose should be followed for 3 months post-delivery (from Day 0 to Month 3 of life).

8.5 Warnings and precautions

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

8.6 Data Monitoring Committee

No Data Monitoring Committee is planned for this trial.

8.7 Steering Committee

A steering committee (SC) will be established comprising investigators participating in the trial, i.e. not being Novartis representatives from the Clinical Trial Team.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the SC will be defined in a SC charter.

9 Data collection and management

9.1 Data confidentiality

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

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

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

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



9.2 Site monitoring

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

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

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

9.3 Data collection

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.

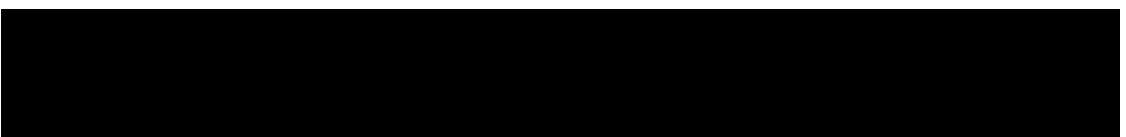
The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate and that entry and updates are performed in a timely manner.

9.3.1 ECG data collection

ECG data will be collected via 12-lead digital ECG machines. The data will be transmitted to an ECG vendor for centralized cardiac safety analysis, as well as further processing and data reconciliation.

9.3.2 IRT data collection

Patient eligibility and enrollment will be tracked using an Interactive Response Technology. The system will be supplied by a vendor, who will also manage the database for that system.



9.3.3 Central laboratory data collection

All laboratory evaluation except urinalysis and urine pregnancy test will be conducted and its data will be collected by the central laboratory.

Designated investigator staff must enter the sample information required by the protocol onto sample collection eCRFs, as well as central laboratory requisition forms. The requisition forms will be printed on 2-part, non-carbon-required paper or will available electronically. If paper forms will be used, one copy of the requisition form will be forwarded to the central laboratory along with the corresponding sample(s), and the other will be retained by the site. CRA will review the central laboratory requisition forms against the sample collection eCRFs for completeness and accuracy, and instruct site personnel to make any required corrections or additions. Further reconciliation of any sample collection data that were collected on both eCRFs and requisition forms will be performed by the designated central laboratory and Novartis.

The samples will be shipped by the site to a designated central laboratory for sample management.

9.4 Database management and quality control

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

Patient numbers and data about all study treatments dispensed to the patient and all IRT assigned dosage changes will be tracked using an Interactive Response Technology. The system will be supplied by a vendor(s), who will also manage the database. The data will be sent electronically to Novartis personnel (or designated CRO).

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

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

10 Statistical methods and data analysis

This is a phase IIIb exploratory study to assess the efficacy and safety of pasireotide in patients with acromegaly inadequately controlled with first generation somatostatin analogues. The data will be analyzed by Novartis and/or designed CRO. It is planned that the data from all centers that participate in this protocol will be used. Continuous variables will be summarized by number of patients, mean, standard deviation, minimum, 25th quantile, median, 75th quantile and maximum. Categorical variables will be summarized by absolute and relative frequencies. Unless otherwise stated, baseline assessment refers to the last assessment prior to the patient's first study drug dose recorded after the signing of the informed consent.



10.1 Analysis sets

10.1.1 Full Analysis Set

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

10.1.2 Safety Set

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

10.1.3 Per-Protocol Set

The Per-Protocol Set (PPS) consists of a subset of the patients in the FAS who are compliant with requirements of the CSP. The protocol deviations criteria will be defined prior to database lock.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data (e.g. age, gender, race, GH levels, standardized IGF-1 levels) will be summarized descriptively for the FAS.

10.3 Treatments (study treatment, concomitant therapies, compliance)

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

These analyses will be performed on the safety set.

10.4 Primary objective

To evaluate the efficacy of pasireotide LAR in patients with acromegaly who are inadequately controlled with currently available somatostatin analogues, as measured by the proportion of patients with GH <1µg/L and IGF-1 <ULN at week 36.



10.4.1 Variable

The variable of interest is proportion of patients who achieved GH <1 μ g/L and IGF-1 <ULN at week 36.

10.4.2 Statistical hypothesis, model, and method of analysis

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

The proportion of patients achieving mean GH levels < 1 μ g/L and IGF-1 <ULN will be calculated along with its two-sided, asymptotic or exact when the criteria for asymptotic approximation were not fulfilled, 95% confidence interval at Week 36.

10.4.3 Handling of missing values/censoring/discontinuations

If a patient has less than three samples for the assessment of the 5-point mean GH from the 2-hour profile, then the mean GH will be considered as missing. Patients with missing GH and or IGF-1 assessment at week 36 will be considered as non-responders.

Multiple imputation method or other adequate methods will be employed to impute missing data and sensitivity analyses will be performed using imputed missing data to assess the robustness of the efficacy findings. The imputation methods as well as sensitivity analyses will be specified in the RAP.

10.4.4 Supporting Analysis of Primary Objective

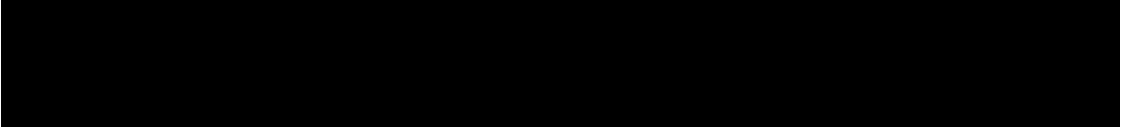
To assess the proportion of patients achieving GH <1 μ g/L and IGF-1 <ULN at weeks 36 by sub-groups of GH level at screening

The proportion of patients who achieved GH <1 μ g/L and IGF-1 <ULN at week 36 among two sub-groups of patients, those having GH level at screening between 1 μ g/L and 2.5 μ g/L, and those having GH level >2.5 μ g/L at screening, will be reported along with their two-sided (exact or asymptotic, depending on assumptions being satisfied) 95% confidence interval.

This supporting analysis is purely exploratory in nature and no statistical multiplicity adjustments will be performed to distinguish it from other endpoints.

10.5 Secondary objectives

The secondary efficacy analysis will be performed on the FAS. The same rule of handling missing values for GH and IGF-1 variables as specified in the analysis of the primary efficacy variable will be used.



10.5.1 Secondary objectives- Core phase

To assess the changes in mean GH from study baseline to week 36

Descriptive summaries of actual and percentage change in GH from study baseline to week 36 values will be provided.

To assess the changes in standardized IGF-1 from study baseline to week 36

Descriptive summaries of actual and percentage change in standardized IGF-1 from study baseline to week 36 values will be provided.

To assess the proportion of patients achieving GH <1 µg/L and IGF-1 <ULN at weeks 12 and 24 overall and by GH level at screening

Proportion of patients who achieved GH <1 µg/L and IGF-1 <ULN at week 12 and 24 will be reported along with its corresponding 95% confidence interval for all patients and also among patients, having GH level at screening between 1 µg/L and 2.5 µg/L, and among patients having GH level at screening > 2.5 µg/L.

To assess the proportion of patients achieving GH <1 µg/L at weeks 12, 24 and 36, overall and by GH level at screening

Proportion of patients who achieved GH <1 µg/L at week 12, 24 and 36 will be reported along with its corresponding 95% confidence interval for all patients and also among patients, having GH level at screening between 1 µg/L and 2.5 µg/L, and patients having GH level at screening > 2.5 µg/L.

To assess the proportion of patients achieving IGF-1 levels <ULN at weeks 12, 24 and 36

Proportion of patients who achieved IGF-1 <ULN at week 12, 24 and 36 will be reported along with its corresponding 95% confidence interval.

To evaluate the effect of pasireotide LAR on HRQoL and signs and symptoms of acromegaly from baseline to weeks 12, 24 and 36

Descriptive statistics, including mean, median, standard deviation, minimum and maximum, will be presented to describe actual standardized scores as measured by HRQoL and changes from baseline to weeks 12, 24 and 36.

For each of the acromegaly symptoms (ring size, headache, fatigue, perspiration, paresthesias, osteoarthralgia), descriptive summaries of actual and changes from baseline to weeks 12, 24 and 36 will be provided. Moreover, shift tables from baseline to the most extreme post-baseline value will also be presented for acromegaly symptoms except ring size

To evaluate the tolerability and safety profile of pasireotide LAR

Same analysis as in [Section 10.5.3](#)

10.5.2 Secondary objectives- Extension phase

To assess the proportion of patients achieving IGF-1 <ULN at weeks 48, 60 and 72

Proportion of patients who achieved IGF-1 <ULN will be calculated along with its two-sided 95% confidence interval at week 48, 60 and 72.

To assess the proportion of patients achieving GH<1 µg/L and IGF-1<ULN at weeks 48, 60 and 72 by treatment with pasireotide LAR alone or with concomitant medications used to treat acromegaly

Proportion of patients who achieved GH<1µg/L and IGF-1<ULN by treatment with pasireotide LAR alone or with concomitant medications used to treat acromegaly will be reported separately along with its corresponding 95% confidence interval at weeks 48, 60 and 72

To assess the proportion of patients achieving GH <1 µg/L at weeks 48, 60 and 72 by treatment with pasireotide LAR alone or with concomitant medications used to treat acromegaly

Proportion of patients who achieved GH<1µg/L by treatment with pasireotide LAR alone or with concomitant medications used to treat acromegaly will be reported separately along with its corresponding 95% confidence interval at weeks 48, 60 and 72

To evaluate the long term effect of pasireotide LAR on HRQoL and signs and symptoms of acromegaly, from baseline and week 36 to week 72

Change in standardized scores as measured by HRQoL and signs and symptoms of acromegaly from baseline and week 36 to week 72.

Descriptive statistics, including mean, median, standard deviation, minimum and maximum, will be presented to describe actual standardized scores as measured by HRQoL and changes from baseline to week 72 and from week 36 to week 72.

For each of the acromegaly symptoms (ring size, headache, fatigue, perspiration, paresthesias, osteoarthralgia), descriptive summaries of actual and changes from baseline to weeks 72, and from week 36 to week 72 will be provided. Moreover, shift tables from baseline to the most extreme post-baseline value, and from week 36 to the most extreme value up to week will also be presented for acromegaly symptoms except ring size.

To evaluate the long term tolerability and safety profile of pasireotide LAR

Same analysis as in [Section 10.5.4](#)

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.

For the core phase, all listings and tables will be presented overall and by maximum dose given. For AEs of special interest, tables will be presented by the given dose as well (AE starts or worsens while the patient is being treated at that dose level.)



For the extension phase, all listings and tables will be presented overall and by type of treatment (monotherapy, combination dopamine agonist, and combination with GH receptor antagonist).

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

1. pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
2. on-treatment period: from day of first dose of study medication to 56 days after last dose of study medication
3. post-treatment period: starting at day 56+1 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-treatment period, the **treatment-emergent** AEs. However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and/or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment overall and by treatment group (described in [Section 10.5.3.2](#) for each phase).

Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event and treatment group (described in [Section 10.5.3.1](#) for each phase).

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

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

10.5.3.3 Laboratory abnormalities

For laboratory tests covered by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, the study's biostatistical and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

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 by-treatment summaries will be generated separately for hematology, biochemistry and urinary laboratory tests:



- shift tables using CTCAE grades to compare baseline to the worst on-treatment value
- for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high)
- 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-treatment result for overall assessments
- listing of ECG evaluations for all patients with at least one abnormality.

Vital signs

Vital signs (body temperature, blood pressure, heart rate) reporting of results will include:

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

Gallbladder

Gallbladder data at each visit will be summarized and listed.

10.5.4 Patient-reported outcomes

AcroQoL total and subscale scores and EQ-5D-5L utility index and VAS scores will be generated in accordance with the respective scoring manual. The FAS will be used for analyzing patient-reported outcome data.

Descriptive statistics will be used to summarize the raw and absolute change from baseline in AcroQoL and EQ-5D-5L scores at each scheduled assessment. Patients with an evaluable baseline score and at least one evaluable post baseline score during the treatment period will be included in the change from baseline analyses.

Missing items data in a scale will be handled based on each instrument manual. All PRO analyses will include data as imputed according to the scoring manual. No imputation will be applied if the total or subscale scores are missing at a visit.

Additional analyses may be performed if deemed necessary. Such analyses will be defined in the RAP.

10.6 Interim analysis

No formal interim analysis will be performed. Primary analysis will occur after all enrolled patients complete the core phase or discontinue prior to complete this phase of the trial. Final analysis will be conducted when all patients complete the extension phase or have discontinued the study prior to completing the extension phase of the trial.

10.7 Sample size calculation

The sample size calculation was based on the primary endpoint (mean GH <1 µg/L and IGF-1 <ULN at week 36). A sample size of 100 patients was chosen to enable the estimation of proportion of patients who achieved biochemical control at week 36 with pasireotide 40-60 mg as 15%, with a precision of 7% for the associated asymptotic two-sided 95% confidence interval.

Considering a drop-out rate of 10%, the sample size required is 112.

Sample size calculation was performed using PASS 2008 software.

10.8 Power for analysis of key secondary variables

Not applicable

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

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

11.2 Responsibilities of the investigator and IRB/IEC/REB

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



11.3 Informed consent procedures

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

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

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

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

11.4 Discontinuation of the study

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

11.5.1 Communication and Publication of Clinical Trial Results

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

Novartis complies with the authorship guidelines of the International Committee of Medical Journal Editors (ICMJE) uniform requirements for manuscripts submitted to biomedical journals and other specific guidelines of the journal or congress to which the document will be submitted. These guidelines apply to any clinical trial publication including but not limited to manuscripts, abstracts, posters, and oral presentations. For more information regarding the ICMJE guidelines, visit ICMJE.org/index.html#author.

Accordingly, ALL AUTHORS MUST HAVE:



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

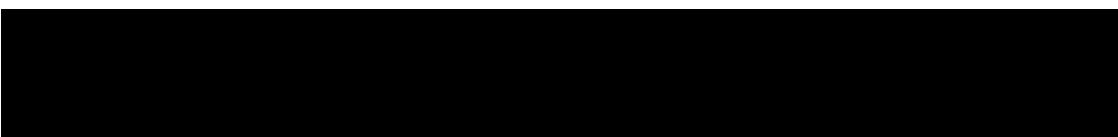
Substantial contribution for primary publication is defined as having active and ongoing participation in the study. Study steering committee members must have significant involvement to study concept, design, and data interpretation and patient recruitment. Each steering committee member must have attended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

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



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

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

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to 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

14.1 Appendix 1: Acromegaly Quality of Life Questionnaire

ACROMEGALY- QUALITY OF LIFE QUESTIONNAIRE
(ACROQoL)

Today's date

Day Month Year

INSTRUCTIONS FOR ANSWERING THE QUESTIONNAIRE

In the following pages there are sentences that describe some of the problems that acromegaly causes to people who, like you, suffer from this illness.

Each sentence is followed by some response options. Some of these refer to the **frequency**, while others refer to **how much you agree or disagree** with them.

Please, read each sentence carefully. Then tick the response option which best describes what you think is happening to you.

Remember that there are NO correct or incorrect answers. We are only interested in what is currently happening to you because of your acromegaly.

It is very important to answer all the questions.

Thank you very much for your collaboration

Because of my Acromegaly...

1. My legs feel weak

• Always

• Most of the time

• Sometimes

• Rarely

• Never

4. I look awful in photographs

• Completely agree

• Moderately agree

• Neither agree nor disagree

• Moderately disagree

• Completely disagree

2. I feel ugly

• Completely agree

• Moderately agree

• Neither agree nor disagree

• Moderately disagree

• Completely disagree

5. I avoid going out very much with friends because of my appearance

• Always

• Most of the time

• Sometimes

• Rarely

• Never

3. I get depressed

• Always

• Most of the time

• Sometimes

• Rarely

• Never

6. I try to avoid socialising

• Always

• Most of the time

• Sometimes

• Rarely

• Never

Because of my Acromegaly...

7. I look different in the mirror

- Completely agree
- Moderately agree
- Neither agree nor disagree
- Moderately disagree
- Completely disagree

10. People stare at me because of my appearance

- Completely agree
- Moderately agree
- Neither agree nor disagree
- Moderately disagree
- Completely disagree

8. I feel rejected by people because of my illness

- Completely agree
- Moderately agree
- Neither agree nor disagree
- Moderately disagree
- Completely disagree

11. Some parts of my body (nose, feet hands,...) are too big

- Completely agree
- Moderately agree
- Neither agree nor disagree
- Moderately disagree
- Completely disagree

9. I have problems carrying out my usual activities (e.g. working, studying, doing household tasks, family or leisure activities)

- Always
- Most of the time
- Sometimes
- Rarely
- Never

12. I have problems doing things with my hands, for example, sewing or handling tools

- Always
- Most of the time
- Sometimes
- Rarely
- Never

Because of my Acromegaly...

**13. The illness affects my performance
at work or in my usual tasks**

- | | | | |
|--------------------|--------------------------|--------------------|--------------------------|
| • Always | <input type="checkbox"/> | • Always | <input type="checkbox"/> |
| • Most of the time | <input type="checkbox"/> | • Most of the time | <input type="checkbox"/> |
| • Sometimes | <input type="checkbox"/> | • Sometimes | <input type="checkbox"/> |
| • Rarely | <input type="checkbox"/> | • Rarely | <input type="checkbox"/> |
| • Never | <input type="checkbox"/> | • Never | <input type="checkbox"/> |

14. My joints ache

**17. It is hard for me to
articulate words due to the size of
my tongue**

- | | | | |
|--------------------|--------------------------|--------------------|--------------------------|
| • Always | <input type="checkbox"/> | • Always | <input type="checkbox"/> |
| • Most of the time | <input type="checkbox"/> | • Most of the time | <input type="checkbox"/> |
| • Sometimes | <input type="checkbox"/> | • Sometimes | <input type="checkbox"/> |
| • Rarely | <input type="checkbox"/> | • Rarely | <input type="checkbox"/> |
| • Never | <input type="checkbox"/> | • Never | <input type="checkbox"/> |

15. I feel tired

**18. I have problems with
sexual relationships**

- | | | | |
|--------------------|--------------------------|--------------------|--------------------------|
| • Always | <input type="checkbox"/> | • Always | <input type="checkbox"/> |
| • Most of the time | <input type="checkbox"/> | • Most of the time | <input type="checkbox"/> |
| • Sometimes | <input type="checkbox"/> | • Sometimes | <input type="checkbox"/> |
| • Rarely | <input type="checkbox"/> | • Rarely | <input type="checkbox"/> |
| • Never | <input type="checkbox"/> | • Never | <input type="checkbox"/> |

Because of my Acromegaly...

19. I feel like a sick person

- Completely agree
- Moderately agree
- Neither agree nor disagree
- Moderately disagree
- Completely disagree

21. I have little sexual appetite

- Always
- Most of the time
- Sometimes
- Rarely
- Never

20. The physical changes produced by my illness govern my life

- Completely agree
- Moderately agree
- Neither agree nor disagree
- Moderately disagree
- Completely disagree

22. I feel weak

- Always
- Most of the time
- Sometimes
- Rarely
- Never

Finally, please check that you have answered all the questions.

Once again thank you very much for your collaboration.

14.2 Appendix 2: Patient Report Outcome Questionnaire EQ-5D5-L

Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY

MOBILITY

- | | |
|----------------------------------|--------------------------|
| I have no problems walking | <input type="checkbox"/> |
| I have slight problems walking | <input type="checkbox"/> |
| I have moderate problems walking | <input type="checkbox"/> |
| I have severe problems walking | <input type="checkbox"/> |
| I am unable to walk | <input type="checkbox"/> |

SELF-CARE

- | | |
|---|--------------------------|
| I have no problems washing or dressing myself | <input type="checkbox"/> |
| I have slight problems washing or dressing myself | <input type="checkbox"/> |
| I have moderate problems washing or dressing myself | <input type="checkbox"/> |
| I have severe problems washing or dressing myself | <input type="checkbox"/> |
| I am unable to wash or dress myself | <input type="checkbox"/> |

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

- | | |
|--|--------------------------|
| I have no problems doing my usual activities | <input type="checkbox"/> |
| I have slight problems doing my usual activities | <input type="checkbox"/> |
| I have moderate problems doing my usual activities | <input type="checkbox"/> |
| I have severe problems doing my usual activities | <input type="checkbox"/> |
| I am unable to do my usual activities | <input type="checkbox"/> |

PAIN / DISCOMFORT

I have no pain or discomfort

The best health
you can imagine

100

I have slight pain or discomfort

95

I have moderate pain or discomfort

90

I have severe pain or discomfort

85

I have extreme pain or discomfort

80

ANXIETY / DEPRESSION

I am not anxious or depressed

75

I am slightly anxious or depressed

70

I am moderately anxious or depressed

65

I am severely anxious or depressed

60

I am extremely anxious or depressed

55

We would like to know how good or bad your health is TODAY.

This scale is numbered from 0 to 100.

100 means the **best** health you can imagine.
0 means the **worst** health you can imagine.

Mark an X on the scale to indicate how your health is TODAY.

Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

The worst health
you can imagine

14.3 Appendix 3: Concomitant Medications with “known risk of TdP (Torsades de pointes)”

The following list of drugs is generally recognized to have a possible association with TdP. This list is not considered to be all inclusive and any questions regarding concomitant medications with known risk of TdP should be discussed with the Novartis global team.

[//crediblemeds.org/](http://crediblemeds.org/)

Clinical Development

Pasireotide / SOM230

Protocol CSOM230C2413 / NCT02354508

A phase IIIb multicenter, open-label, single arm study to evaluate the efficacy and safety of pasireotide in patients with acromegaly inadequately controlled with first generation somatostatin analogues

Authors



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List of abbreviations

AcroQoL	Acromegaly Quality of Life
ACTH	Adrenocorticotropic Hormone
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
Anti-HBc	Anti-Hepatitis B core
Anti-HCV	Anti-Hepatitis C Virus
Anti-HEV	Anti-Hepatitis E Virus
APTT	Partial Thromboplastin Time
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATC Class	Anatomical Therapeutic Chemical Classification System
ATG	Autogel
B-hCG	β-subunit of hCG gonadotropin
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CPK	Creatine Phosphokinase
CPO	(Novartis) Country Pharma Organization
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSR	Clinical study report
CSR addendum	An addendum to Clinical Study Report (CSR) that captures all the additional information that is not included in the CSR
CTCAE	Common Toxicity Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DM	Diabetes Mellitus
DMC	Data Monitoring Committee
DS&E	Drug Safety and Epidemiology
EBV	Epstein Barr Virus
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GH	Growth Hormone
GIP/GLP	Gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1
HbA1C	Hemoglobin A1c
Hbs-Ag	Hepatitis B surface-Antigen
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
HRQoL	Health Related Quality of Life
i.m.	Intramuscular
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IGF	Insulin-like Growth Factor

IgM	Immunoglobulin M
IMS	Integrated Medical Safety
IRB	Institutional Review Board
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
ITT	Intention To Treat
IUD	Intrauterine Device
IUS	Intrauterine System
LAR	Long Acting Release
LDH	Lactic Dehydrogenase
LDL	Low Density Lipoprotein
LFT	Liver Function Testing
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-CTCAE v.4.03	National Cancer Institute-Common Toxicity Criteria Adverse Event version 4.03
OGTT	Oral Glucose Tolerance Test
PCR	Polymerase Chain Reaction
PHI	Protected Health Information
PK/PD	Pharmacokinetic/Pharmacodynamic
PRL	Prolactin
PRO	Patient Reported Outcomes
PT	Prothrombin Time
PTT	Partial Thromboplastin time
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
REB	Research Ethics Board
s.c.	Subcutaneous
SAE	Serious Adverse Event
SC	Steering Committee
SmPc	Summary of Product Characteristics
SOP	Standard Operating Procedure
SSA	Somatostatin analogues
sst	somatostatin receptor subtype
TdP	Torsades de pointes
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit Normal
γ-GT	Gamma-Glutamyltransferase

Glossary of terms

Assessment	A procedure used to generate data required by the study
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Patient Number	A unique identifying number assigned to each patient/subject/healthy volunteer 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, unless the patient will be followed for progression and/or survival
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Treatment group	A treatment group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. Cohorts are not expanded, new cohorts are enrolled.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

Amendment 1

Amendment rationale

The main purpose of this amendment is to:

- To reference the octreotide summary of product characteristics (SmPc) for guidance on dosing modifications and safety reporting [REDACTED]
- Update the safety section to reflect changes made to version 15 of the Investigator's Brochure, specifically to the Referenced Safety Information Section and the reporting of suspected unexpected serious adverse reactions.
- To extend the safety follow-up of patients from 8 weeks to 12 weeks (5 half-lives of pasireotide LAR).
- To allow dose reductions in patients with controlled GH values, in whom treatment reduced IGF-1 values to below the lower limit of normal since this could lead to adverse events.
- To add a recommendation for additional assessments of electrolytes. The use of medications with conditional risk for Torsade des Pointes and congenital long QT interval are permitted per protocol and several medications (e.g. diuretics) from these drug classes have the potential to decrease the potassium level. Therefore, additional monitoring of electrolytes as clinically indicated to the already frequent electrolyte monitoring as per protocol is recommended.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions. The major changes to the protocol, and the sections affected, are detailed below:

1. **Protocol Summary:** Corrected a typographical error in the number of weeks for the extension period from 76 weeks to 72 weeks.
2. **Protocol Summary:** Update the safety follow-up period from the last dose of study medication from 8 weeks to 12 weeks (84 days) (5 half-lives of pasireotide LAR).
3. **Section 4.1** Run-in phase: Updated the language to clarify that patients will receive octreotide LAR 40 mg every 4 weeks. After 3 months of treatment have been completed, and prior to the fourth injection (at visit 5), mean GH and IGF-1 will be assessed.
4. **Section 4.1** Safety follow-up: Update the safety follow-up period from the last dose of study medication from 8 weeks to 12 weeks (84 days) (5 half-lives of pasireotide LAR).
5. **Section 6.1.1** Dosing regimen: **Table 6-1** has been updated to include the 10mg dose of pasireotide LAR that will now be permitted for dose reductions.
6. **Section 6.2.1** Dose Modifications and Dose Delays: Down titrations of pasireotide LAR (from 60 mg to 40 mg, from 40 mg to 20 mg and from 20 mg to 10 mg) are permitted for patients with IGF-1 values that fall below the lower limit of normal and have controlled mean GH levels. The IGF-I values are required to be confirmed to be below LLN on two consecutive assessments; when IGF-I is found to be decreased to <LLN, a repeat measurement will be performed at the following visit for confirmation purposes. If [REDACTED]

biochemical control is maintained, the patient can continue on the lower dose for the remainder of the trial. If biochemical control is lost, the dose should be increased to the immediate previous dose administered.

7. **Section 6.2.1** Treatment Duration: Included guidance on dosing modifications and safety reporting for octreotide LAR, investigators should follow the summary of product characteristics (SmPc).
8. **Section 6.3.1.1:** Added a recommendation for more frequent monitoring of electrolytes as clinically indicated in patients treated with medications that may decrease potassium levels (e.g. diuretics).
9. **Section 6.5** Study drug preparation and dispensation: Added information on the preparation of the octreotide LAR dose and that the package insert should be referenced for further information.
10. **Section 7.1** Study Flow and Visit Schedule: Added the flexibility for a +/-2 day window for the screening visit.
11. **Section 7.1.2** Screening: The language has been updated to clarify that patients can be re-screened as long as the cause of the screen failure is normal GH and/or IGF-1 values, patients can be rescreened once these parameters go beyond the control level, the patient has continued to receive scheduled injection of the SSAs and had at least a 3-month treatment with maximal doses of first generation SSAs. The protocol will also limit the number of times a patient can be re-screened to 2 times, and Novartis must be informed of the intent to re-screen a patient.
12. **Section 8.1.3** Adverse Events of Special Interest: The section has been modified to indicate that the list of AEs considered special interest provided in the protocol is not all inclusive and can be modified throughout the lifetime of the trial.
13. **Section 8.2.2** Reporting: The language was updated to ensure reporting of SAEs 84 days after the patient has stopped study drug administration. Also any SAEs experienced after the 84 days should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.
14. **Section 8.2.2** Reporting: The language was updated to state that if an SAE is not present in the Reference Safety Information section of the Investigator's Brochure (unexpected) and is thought to be related to the Novartis study treatment (suspected), an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. 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. 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.
15. **Appendix 14.4** Pharmacy instructions for pasireotide LAR: This appendix was added to provide instructions on how to prepare the study doses of pasireotide LAR.

IRB/IEC 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.



Protocol summary:

Protocol number	CSOM230C2413
Title	A phase IIIb multicenter, open-label, single arm study to evaluate the efficacy and safety of pasireotide in patients with acromegaly inadequately controlled with first generation somatostatin analogues
Brief title	Study of efficacy and safety of pasireotide LAR in patients with inadequately controlled acromegaly
Sponsor and Clinical Phase	Novartis, Phase IIIb
Investigation type	Drug
Study type	Interventional
Purpose and rationale	To evaluate the efficacy and safety of pasireotide, a second generation somatostatin analogue with a broader affinity to sst receptors, in patients with in adequately controlled acromegaly after a minimum of 3 months with high doses of first generation somatostatin analogues.
Primary Objective(s)	<p>Primary Objective To evaluate the efficacy of pasireotide LAR in patients with acromegaly who are inadequately controlled with currently available somatostatin analogues, as measured by the proportion of patients with GH <1µg/L and IGF-1 <ULN at week 36 overall and by mGH level at screening.</p> <p>Supporting Analysis for Primary To assess the proportion of patients achieving GH <1µg/L and IGF-1 <ULN at week 36 by GH level at screening.</p>
Secondary Objectives	<p>Core Phase To assess the changes in mean GH from study baseline to week 36. To assess the changes in standardized IGF-1 from study baseline to week 36. To assess the proportion of patients achieving GH <1 µg/L and IGF-1 <ULN at weeks 12 and 24 overall and by GH level at screening To assess the proportion of patients achieving GH <1µg/L at weeks 12, 24 and 36, overall and by GH level at screening To assess the proportion of patients achieving IGF-1 levels <ULN at weeks 12, 24 and 36 To evaluate the tolerability and safety profile of pasireotide LAR To evaluate the effect of pasireotide LAR on HRQoL and signs and symptoms of acromegaly from baseline to weeks 12, 24 and 36</p> <p>Extension Phase To assess the proportion of patients achieving GH <1 µg/L and IGF-1 <ULN overall and by GH level at screening at weeks 48, 60 and 72 during the treatment with pasireotide LAR monotherapy To evaluate the long term tolerability and safety profile of pasireotide LAR To evaluate the long term effect of pasireotide LAR on HRQoL and signs and symptoms of acromegaly, from baseline and week 36 to week 72</p>
Study design	<p>Group 1 – Patients treated with octreotide LAR 30mg from the countries where octreotide LAR 40mg is approved for the treatment of acromegaly at the time of screening – Patients participate in the run-in phase.</p> <p>Run-In phase (Screening to Baseline) Patients will start treatment with octreotide LAR 40 mg every 4 weeks. Patients who have not achieved biochemical control after 3 injections can be enrolled in the study.</p> <p>Core Phase (Baseline to week 36) Patients will start treatment on pasireotide LAR 40 mg every 4 weeks until week 32. A mean GH value and IGF-1 value will be assessed every 12 weeks until week 36. The dose can be adjusted after the evaluation of biochemical control. During the core phase any acromegaly concomitant medication is prohibited.</p>

	<p>Extension Phase (week 36 to week 72) Patients will receive the same dose of pasireotide LAR at week 36, which is the first dose of study medication in the extension phase. At week 40 the dose can be adjusted and acromegaly concomitant medication can be added to the treatment if, patients remain uncontrolled. Patients will receive pasireotide LAR 40mg/60mg until week 68 for a total of 32 weeks in the extension phase. A mean GH value and IGF-1 value will be assessed every 12 weeks until week 72.</p> <p>Safety follow-up After discontinuation or completion of study treatment, all patients will be followed for safety 12 weeks (84 days) weeks after the last study drug administration.</p> <p>Group 2 – Patients treated with octreotide 30 mg from countries where octreotide 40mg has NOT been approved for the treatment of acromegaly at screening or patients treated with octreotide 40mg or lanreotide 120mg - Patients who do not have the run-in phase.</p> <p>Core Phase (Baseline to week 36) Same procedure to be followed as Group1</p> <p>Extension Phase (week 36 to week 72) Same procedure to be followed as Group1</p> <p>Safety follow-up Same procedure to be followed as Group1</p>
Population	<p>The eligible patient population will consist of inadequately controlled acromegalic patients with first generation somatostatin analogues. The study will enroll a total number of 112 patients.</p>
Inclusion criteria	<p>Patients eligible for inclusion in this study have to meet all of the following criteria:</p> <ol style="list-style-type: none"> 1. Written informed consent must be obtained prior to any screening procedures 2. Male and female patients ≥ 18 years of age 3. Patients with confirmed diagnosis of inadequately controlled acromegaly as evidenced by the following: <ul style="list-style-type: none"> • A mean GH concentration of a 5-point profile over a 2-hour period ≥ 1 $\mu\text{g/L}$ and sex- and age-adjusted IGF-1 $>1.3 \times \text{ULN}$ 4. Patients treated with high doses of octreotide LAR (30 mg or 40 mg) or lanreotide ATG (120 mg) given as monotherapy for at least 3 months prior to screening (Visit 1) <ul style="list-style-type: none"> • Note: Patients currently being treated with octreotide LAR 30mg from countries where the 40 mg dose is approved at the time of screening will start a run- in phase which they will receive the 3 injections of octreotide LAR 40 mg before being evaluated for eligibility for the core phase of the study
Exclusion criteria	<p>Patients eligible for this study must not meet any of the following criteria:</p> <ol style="list-style-type: none"> 1. Concomitant treatment with other medications known to reduce GH and or IGF-1, other than octreotide LAR or lanreotide ATG, unless it discontinued 3 months prior to visit 1 (screening) 2. Patients with compression of the optic chiasm causing any visual field defect that requires surgical intervention 3. Diabetic patients with poor glycaemic control as evidenced by HbA1c $>8\%$ at visit 1 (screening) 4. Patients who are hypothyroid and not on adequate replacement therapy 5. Patients with symptomatic cholelithiasis and acute or chronic pancreatitis 6. Patients with clinically significant valvular disease 7. Patients with risk factors for torsade de pointes, i.e. patients with a baseline QTcF >450 ms in males, and >460 ms in females 8. Hypokalaemia, hypomagnesaemia, uncontrolled hypothyroidism, family history of long QT syndrome or concomitant medications with known risk of TdP. Drugs with possible risk of TdP should be avoided whenever feasible. 9. Patients who have congestive heart failure (NYHA Class III or IV), unstable

	<p>angina, sustained ventricular tachycardia, clinically significant bradycardia, advanced heart block, history of acute MI less than one year prior to study entry or clinically significant impairment in cardiovascular function.</p> <p>10. Concomitant disease(s) that could prolong the QT interval such as autonomic neuropathy (caused by diabetes or Parkinson's disease), HIV, cirrhosis, uncontrolled hypothyroidism or cardiac failure</p> <p>11. Patients with liver disease such as cirrhosis, chronic active hepatitis, or chronic persistent hepatitis, or patients with ALT/AST > 2.0 X ULN, serum bilirubin >2.0 X ULN</p> <p>12. Presence of Hepatitis B surface antigen (HbsAg) or Hepatitis C antibody test (anti-HCV)</p> <p>13. Patients with serum creatinine >2.0 X ULN</p> <p>14. Patients with WBC <3 X 10⁹/L; Hb 90% < LLN; PLT <100 X 10⁹/L</p> <p>15. Patients with the presence of active or suspected acute or chronic uncontrolled infection</p> <p>16. Patients who have undergone major surgery/surgical therapy for any cause within 4 weeks prior to visit 1 (screening)</p> <p>17. Patients with active malignant disease within the last five years (with the exception of basal cell carcinoma or carcinoma in situ of the cervix)</p> <p>18. 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)</p> <p>19. History of syncope or family history of idiopathic sudden death</p> <p>20. History of immunocompromise, including a positive HIV test result (ELISA and Western blot). A HIV test will not be required; however, previous medical history will be reviewed</p> <p>21. Known hypersensitivity to somatostatin analogues or any other component of the pasireotide LAR</p> <p>22. Patients who have a history of alcohol or drug abuse in the 6 month period prior to receiving pasireotide</p> <p>23. Patients who have given a blood donation (of 400 ml or more) within 2 months before receiving pasireotide</p> <p>24. Patients who have participated in any clinical investigation with an investigational drug within 1 month prior to dosing</p> <p>25. Patients with any current or prior medical condition that, in the judgment of the investigator may interfere with the conduct of the study or the evaluation of the study results</p> <p>26. 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.</p> <p>27. Sexually active males unless they use a condom during intercourse while taking drug and for 3 months following last dose of pasireotide 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.</p> <p>28. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.</p> <p>29. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and 3 months following the last dose of pasireotide. Highly effective contraception methods include:</p> <ul style="list-style-type: none">• Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception• Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment• Male sterilization (at least 6 months prior to screening). For female subjects on the study the vasectomized male partner should be the sole partner for that subject.• Combination of any two of the following (a+b or a+c, or b+c):<ul style="list-style-type: none">a. Use of oral, injected or implanted hormonal methods of contraception or
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	<p>other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.</p> <p>b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)</p> <p>c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository</p> <p>In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.</p> <p>Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.</p>
Investigational and reference therapy	pasireotide LAR 40mg and 60mg, octreotide LAR 40mg
Efficacy assessments	<ul style="list-style-type: none"> • A 5-point GH • IGF1 • Acromegaly symptoms • Health-related Quality of Life
Safety assessments	<ul style="list-style-type: none"> • Physical examination • Vital signs • Laboratory evaluations (hematology, clinical chemistry, liver function testing, coagulation, urinalysis) • Pregnancy • Gallbladder ultrasound • Cardiac assessments
Other assessments	NA
Data analysis	<p>The primary variable is the proportion of patients who achieved GH < 1μg/L and IGF-1 < ULN at week 36. This proportion will be provided along with its asymptotic (or exact, depending on the sample size) 95% CI. Secondary objectives which are measured by proportions will be similarly reported. Descriptive summaries of actual and percentage change in GH, actual and percentage change in standardized IGF-1, from study baseline to week 36 values will be provided. Change in standardized scores as measured by HRQoL and signs and symptoms of acromegaly from baseline and week 36 to week 72 will be provided.</p>
Key words	acromegaly, pasireotide LAR, octreotide LAR, 5-point GH, IGF-1

1 **Background**

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Acromegaly is a rare growth disorder characterized by a clinical syndrome resulting primarily from the effects of excess growth hormone (GH) and insulin-like growth factor 1 (IGF-1) on various organ systems. Acromegaly is caused by a GH-secreting pituitary adenoma in more than 90% of patients. The prevalence of acromegaly is estimated to be 40 to 70 cases per million, with an annual incidence of 3 to 4 new cases per million ([Holdaway and Rajasoorya 1999](#)). However, recent studies suggest that pituitary adenomas may be more prevalent than previously thought, and that the prevalence of acromegaly may be well over 100 cases per million ([Rosario 2011, Daly et al 2006](#)).

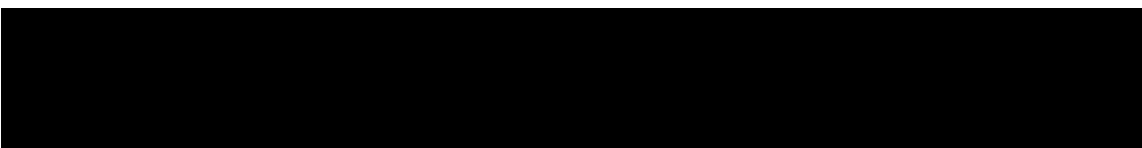
The clinical manifestations of acromegaly are due to the peripheral actions of the GH excess and elevated IGF-1 concentrations and/or local tumor mass effect. The symptoms and signs of acromegaly can be divided into 3 categories: physical changes due to excessive amounts of GH and IGF-1, metabolic effects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

The therapeutic goals in acromegaly are to reduce mortality to the expected age and sex adjusted rates by using treatments that remove the tumor mass and/or control its growth and restore GH secretion and action to normal. In the past, the biochemical goals of therapy were to reduce the circulating IGF-1 levels to normal for age and sex and to reduce serum GH concentrations to <2.5 µg/L (mean GH concentration of a 5-point profile within a 2-hour time period) or to less than 1 µg/L after an oral glucose load ([Giustina et al 2000](#)). Current guidelines recommend GH levels <1 µg/L and normalization of IGF-1 as biochemical goals of therapy ([Melmed et al 2010](#)).

Treatment modalities for acromegaly include surgery, radiotherapy or treatment with drugs.

Surgery: transphenoidal surgery is the most frequently recommended treatment however surgical effectiveness varies depending on expertise in pituitary surgery, on the size and extension of the anatomic mass, and the preoperative levels of GH. 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 throughout their lifespan 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 medications. 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 drugs in rare cases as primary treatment. It is usually reserved 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 over a 2-year timeframe, although late effects can occur in some cases. Radiation therapy causes 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: the medical treatment options for acromegaly include somatostatin analogues, growth hormone antagonists and dopamine agonists.

Somatostatin analogues have proven to be safe, well-tolerated and effective and are the medical treatment of choice for patients with acromegaly. The currently marketed somatostatin analogues are octreotide (Sandostatin®) and lanreotide (Somatuline®). Octreotide has been available for over 20 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 treatment(s) and other study treatment(s)

1.2.1 Overview of pasireotide (SOM230)

Pasireotide (SOM230) is a cyclohexapeptide, SSA with the following chemical name: (2-Aminoethyl)carbamic acid (2R,5S,8S,11S,14R,17S,19aS)-11-(4-aminobutyl)-5-benzyl-8-(4-benzyloxybenzyl)-14-(1H-indol-3ylmethyl)-4,7,10,13,16,19-hexaoxo-17-phenyloctadecahydro-3a,6,9,12,15,18-hexaazacyclopentacyclooctadecen-2-yl ester, di[(S)-2aminosuccinic acid] salt. Like natural somatostatin and other SSAs, pasireotide exerts its pharmacological activity via binding to somatostatin receptors (sst.). Somatostatin is an endogenous peptide that modulates a number of exocrine and endocrine secretions. There are five known somatostatin receptors: sst1, 2, 3, 4 and 5 as outlined in Table 1-1. When compared to octreotide, pasireotide has a binding affinity which is 30-40 times greater for sst1 and sst5, 5 times greater for sst3, and a comparable affinity for sst2 (Schmid and Brueggen 2012). Somatostatin receptors are expressed in different tissues under normal physiological conditions as well as in many solid tumors, especially in neuroendocrine tumors where hormones are excessively secreted, e.g. acromegaly, gastroenteropancreatic neuroendocrine tumor (GEP/NET) and Cushing's disease (Freda 2002, Oberg et al 2004 and Van der Hoek et al 2005). A detailed summary of available preclinical data is provided in the current [Investigator's Brochure].

Table 1-1 Binding profiles for octreotide and pasireotide at hsst1-5 (IC50, mol/L)

Compound	sst1	sst2	sst3	sst4	sst5
Octreotide acetate (SMS995)	2.8x10 ⁻⁷	3.8x10 ⁻¹⁰	7.1x10 ⁻⁹	>10 ⁻⁶	6.3x10 ⁻⁹
Pasireotide (SOM230)	9.3x10 ⁻⁹	1.0x10 ⁻⁹	1.5x10 ⁻⁹	>10 ⁻⁶	1.6x10 ⁻¹⁰
Ratio of IC ₅₀ :octreotide acetate/pasireotide (SMS995/SOM230)	30	0.4	5	--	39

1.2.1.1 Non-clinical experience

Preclinical data on binding affinity and functional activity in vitro and efficacy on hormone secretion in vivo have been obtained with the s.c. formulation in rats, dogs, mice and monkeys. Long-term in vivo studies performed using drug application by osmotic mini-pumps (Bruns 2002, Weckbecker 2002) have shown not only that the inhibitory effect of pasireotide was stronger, but also that there was less response escape (Bruns 2002) and (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.

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

1.2.1.2 Clinical experience

The clinical development program for pasireotide has focused on endocrine-related pathologies. Two formulations of pasireotide are currently in development: an immediate release formulation for subcutaneous (s.c.) injection and a long-acting release (LAR) formulation for i.m. injection. These formulations have been characterized by Phase 1 studies in healthy volunteers, and Phase 1 - 3 studies in patients with acromegaly, Cushing's disease, and gastroenteropancreatic neuroendocrine tumors.

The pasireotide s.c. formulation (Signifor®) is currently approved in more than 50 countries worldwide for the treatment of Cushing's disease.

The efficacy and safety of pasireotide LAR in acromegaly are primarily derived from two large, randomized Phase 3 studies comparing pasireotide LAR with active controls (superiority design):

- Study [SOM230C2305] compared pasireotide LAR with octreotide LAR in medically naïve patients with active acromegaly. In this study, pasireotide LAR was shown to be significantly superior to octreotide LAR for the treatment of acromegaly in medically naïve patients in terms of biochemical control (GH < 2.5 µg/L and normalization of IGF-1 levels) (31.3% vs. 19.2%; p-value 0.007), providing higher response rate in both de novo patients and in patients with prior pituitary surgery (25.7% vs. 17.3% in de novo patients; 39.4% vs. 21.8% in post-surgical patients). Pasireotide LAR was as effective as octreotide LAR in reducing tumor volume, improving acromegaly symptoms and ring size, and quality of life [CSOM230C2305].
- Study [SOM230C2402] compared double-blind pasireotide LAR 40 mg and pasireotide LAR 60 mg with open-label octreotide LAR or lanreotide ATG—active control - in patients with inadequately controlled acromegaly. This study showed that both pasireotide LAR doses (40 mg and 60 mg) are superior to active control (octreotide LAR 30 mg or lanreotide ATG 120 mg). The proportion of responders at Week 24 was significantly higher with pasireotide LAR 40 mg (15.4%, 95% CI 7.63, 26.48) and pasireotide LAR 60 mg (20.0%, 95% CI 11.10, 31.77) than in patients who continued their previous treatment (0%) (p=0.0006 and <0.0001 for pasireotide LAR 40 mg and 60 mg, respectively). Both pasireotide doses were superior to active control in normalizing IGF-1 levels and in

reducing GH to <2.5 µg/L. The proportion of patients with a reduction of GH to <2.5 µg/L at Week 24 was highest in the pasireotide LAR 60 mg arm (43.1%), followed by the pasireotide LAR 40 mg arm (35.4%), and the active control arm (13.2%) The proportion of patients who achieved normalization of IGF-1 at Week 24 (key secondary efficacy variable) was significantly higher in both pasireotide arms (24.6% and 26.2% responders) compared to the active control arm (zero responders)

The safety of pasireotide has been well characterized in 491 patients with acromegaly (419 patients using the LAR formulation, and 72 patients using the s.c. formulation). In addition, pasireotide s.c. and LAR formulations have been used in over 750 other subjects including healthy volunteer and special safety studies. The safety findings in patients with acromegaly are in line with expected pharmacodynamic effects of pasireotide, based on both preclinical and clinical experience, and are consistent with the known side effects of approved SSAs (with the exception of an increased incidence and magnitude of hyperglycemia)

A detailed summary of the clinical data (including safety and PK) is provided in the current [Investigator's Brochure].

2 Rationale

2.1 Study rationale and purpose

Pasireotide (SOM230) is a second generation SSA with a higher affinity to a greater number of somatostatin receptors compared to octreotide and lanreotide, which results in improved efficacy in acromegaly. Pituitary GH-secreting tumors primarily express SSTR2 and 5 (and to a lesser extent SSTR1 and 3). The currently available SSAs octreotide and lanreotide have high affinity for SSTR2, and low affinity for the remaining receptor subtypes. Although SSTR2 is considered the pivotal receptor subtype for regulation of GH secretion, its expression is variable and this may at least in part explain resistance or partial response to octreotide or lanreotide therapy observed in some patients. Recent data suggest that approximately 50% of the patients are not biochemically controlled with currently available SSAs ([Carmichael et. al 2014](#)). In a recently completed phase III study in medically naive acromegalic patients, the largest in this population, 19% of patients treated with octreotide LAR achieved biochemical control after one year of treatment.

Results of clinical studies currently available with pasireotide indicate that it is a safe and effective treatment in patients with acromegaly. The purpose of this study is to evaluate the efficacy and safety of pasireotide LAR, in patients with acromegaly who are inadequately controlled after a minimum of 3 months with maximal approved doses of first generation somatostatin analogues (octreotide LAR 30 mg or 40 mg- depending on the country - or lanreotide ATG 120mg). The recently completed SOM230C2402 study in biochemically uncontrolled patients after at least 6 months of treatment with high doses of octreotide LAR or lanreotide ATG showed that no further benefit was achieved when this therapy was continued with patients achieving neither biochemical control nor normal IGF-1. Therefore, an earlier treatment change to pasireotide LAR might be beneficial for these patients.

In addition, a new consensus has been reached on the definition of controlled acromegaly: GH<1.0 µg/L in association with normal IGF-I levels ([Giustina et al 2014](#)). Therefore, the

new study will enrol patients that satisfy the new criteria of uncontrolled acromegaly – GH \geq 1.0 μ g/L and IGF-I $>$ 1.3xULN - and it will provide data not only in the patients with a GH $>$ 2.5 μ g/L but also, for the first time, in the patients with a GH level between 1.0 and 2.5 μ g/L that are known to represent a large group of patients with inadequately controlled acromegaly.

2.2 Rationale for the study design

The study is an open-label, single-arm; multi-centre international study to evaluate the safety and the efficacy of pasireotide LAR in patient with inadequately controlled acromegaly after a minimum of 3 months with high doses of the first generation somatostatin analogues.

A single-arm, open-label study design was chosen since the objective of this study is to obtain further data of the efficacy and safety of pasireotide LAR in patients with acromegaly, but not as confirmation of efficacy. Efficacy of pasireotide in patients not controlled with other somatostatin analogues was already demonstrated in Study [CSOM230C2402], a double-blinded controlled study, in which patients randomized to the active control (octreotide LAR 30mg or lanreotide ATG 120mg) did not achieve biochemical control with further treatment whereas patients randomly allocated to pasireotide LAR 40 mg or 60 mg were able to achieve biochemical control for the very first time. Additionally, the natural history of the disease is well understood and placebo effects on efficacy evaluations are negligible.

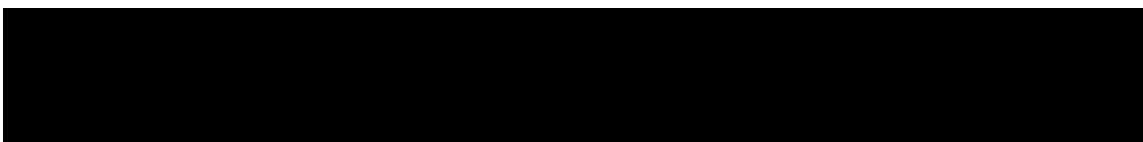
The primary objective of the study was chosen based on the new published criteria for diagnosis and management of acromegaly (Giustina et al 2014). Elevated GH and IGF-1 levels are predictors of mortality, and lowering GH and normalizing IGF-1 results in mortality rates similar to those expected in the general population. The definition of a safe GH level was updated, due to the new more sensitive and specific assays. This new guideline recommends reducing GH to levels as close to normal as possible. According to this consensus document optimal disease control is now defined as IGF-1 level in the sex and age-adjusted normal range and a GH level less than 1.0 μ g/L. This data will complement the results obtained in study C2402, where patients achieving the previous definition of biochemical control (i.e. GH levels $<$ 2.5 μ g/L and normalization of IGF-1) were reported.

2.3 Rationale for dose and regimen selection

The pasireotide LAR dose for acromegaly patients is based on the study CSOM230C2305. It was a multi-center, randomized, blinded study to assess the safety and efficacy of pasireotide LAR vs. octreotide LAR in patients with active acromegaly. The results of the study demonstrated that pasireotide LAR 40 mg every 28 days is superior to octreotide LAR 20 mg every 28 days in providing biochemical control in patients with medically naïve acromegaly i.e., suppression of GH levels to $<$ 2.5 μ g/L and normalization of IGF-1 [CSOM230C2305]. Patients enrolled in this study will start with pasireotide LAR 40 mg every 28days.

Study [CSOM230C2402] demonstrated that both doses of pasireotide LAR 40mg and 60 mg are efficacious in patients inadequately controlled on octreotide LAR and lanreotide ATG.

Based on these data, patients should be evaluated for clinical benefit 3 months (84 days) after the start of pasireotide LAR 40 mg (i.m.) therapy. A dose increase to 60 mg every 28 days will be mandated after 12 weeks of pasireotide LAR treatment if adequate levels of GH and



IGF-1 are not observed with the 40 mg dose (no reduction of mean GH level to < 1.0 μ g/L and no decrease of IGF-1 to within normal limits (age and sex related) and provided there are no safety concerns.

Management of suspected adverse reactions may require temporary dose reduction of pasireotide LAR. Dose reduction by decrements of 20 mg every 28 days is recommended. Dose increase and dose reduction is to be based on investigator's assessment of risk and benefit for the patient.

In the case of octreotide LAR, in order to be enrolled in the study, patients should have been treated with 30 or 40 mg for at least three months and not achieved biochemical control. Octreotide LAR 30mg has been approved and available for over 20 years: octreotide LAR 40mg is not approved/available in all countries. Patients enrolled in countries where the 40mg dose is approved, must be treated with this dose prior to enrollment or during the run-in phase of the study.

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.

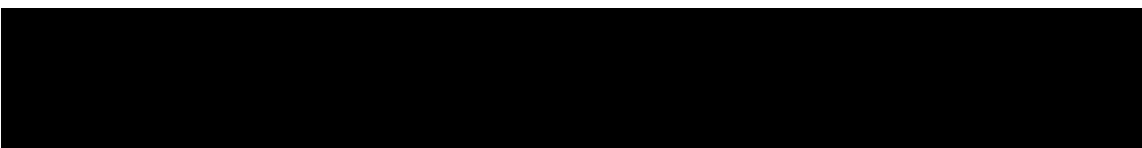


Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
To evaluate the efficacy of pasireotide LAR in patients with acromegaly who are inadequately controlled with maximal approved doses of currently available somatostatin analogues, as measured by the proportion of patients with GH <1 μ g/L and IGF-1 <ULN at week 36	Proportion of patients who achieved GH <1 μ g/L and IGF-1 <ULN at week 36.	
Supporting Analysis for Primary		Refer to Section 10.4.4
To assess the proportion of patients achieving GH <1 μ g/L and IGF-1 <ULN at week 36 by GH level at screening.	Proportion of patients who achieved GH <1 μ g/L and IGF-1 <ULN at week 36 in patients having GH level at screening between 1 μ g/L and 2.5 μ g/L, and in patients having GH level at screening >2.5 μ g/L	
Secondary- core phase		Refer to Section 10.5.1
To assess the changes in mean GH from study baseline to week 36	Changes in mean GH from study baseline to week 36.	
To assess the changes in standardized IGF-1 from study baseline to week 36	Changes in standardized IGF-1 from study baseline to week 36.	
To assess the proportion of patients achieving GH <1 μ g/L and IGF-1 <ULN at weeks 12 and 24 overall and by GH level at screening	Proportion of patients who achieved GH <1 μ g/L and IGF-1 <ULN at week 12 and 24 overall and by GH level at screening.	
To assess the proportion of patients achieving GH <1 μ g/L at weeks 12, 24 and 36, overall and by GH level at screening	Proportion of patients who achieved GH <1 μ g/L at week 12, 24 and 36 overall and by GH level at screening.	
To assess the proportion of patients achieving IGF-1 levels <ULN at weeks 12, 24 and 36	Proportion of patients who achieved IGF-1 <ULN at week 12, 24 and 36.	
To evaluate the tolerability and safety profile of pasireotide LAR	Toxicity will be assessed using the National Cancer Institute-Common Toxicology Criteria Adverse Events version 4 (NCI-CTCAE v.4.03) and for laboratory assessments that include biochemistry, hematology, urinalysis; special safety assessments that include the regular monitoring and recording of blood glucose, insulin, HbA1c, GH and IGF-1, thyroid and liver function tests, gallbladder examinations and ECGs. Concomitant medications/Significant nondrug therapies will be assessed from study enrollment until the safety follow-up.	
To evaluate the effect of pasireotide LAR on HRQoL and signs and symptoms of acromegaly from baseline to weeks 12, 24 and 36	Change in scores as measured by AcroQoL, EQ-5D-5L and signs and symptoms of acromegaly from baseline to weeks 12, 24 and 36	

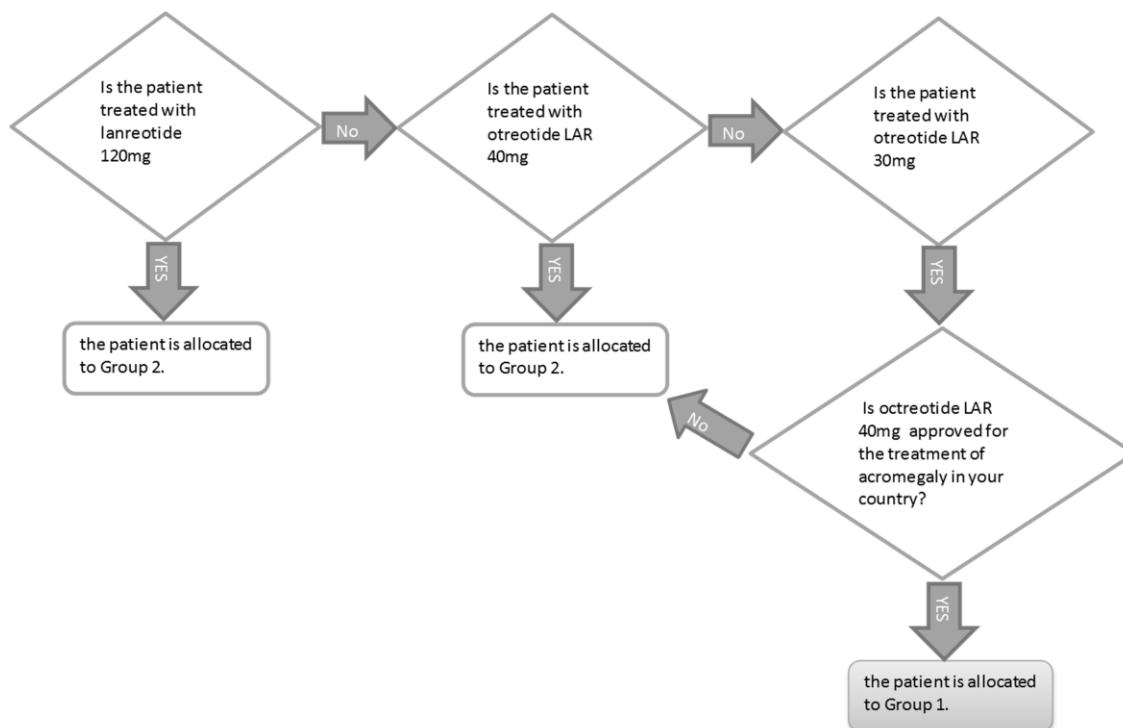
Objective	Endpoint	Analysis
Secondary – extension phase		Refer to Section 10.5.2
To assess the proportion of patients achieving IGF-1 <ULN at weeks 48, 60 and 72	Proportion of patients who achieved IGF-1 <ULN at weeks 48, 60 and 72	
To assess the proportion of patients achieving GH <1 µg/L and IGF-1 <ULN at weeks 48, 60 and 72 by treatment with pasireotide LAR alone or with concomitant medications used to treat acromegaly	Proportion of patients who achieved GH <1 µg/L and IGF-1 <ULN at weeks 48, 60 and 72 by treatment with pasireotide LAR alone or with concomitant medications used to treat acromegaly	
To assess the proportion of patients achieving GH <1 µg/L at weeks 48, 60 and 72 by treatment with pasireotide LAR alone or with concomitant medications used to treat acromegaly	Proportion of patients who achieved GH <1 µg/L at weeks 48, 60 and 72 by treatment with pasireotide LAR alone or with concomitant medications used to treat acromegaly	
To evaluate the long term tolerability and safety profile of pasireotide LAR	Toxicity will be assessed using the National Cancer Institute-Common Toxicology Criteria Adverse Events version 4 (NCI-CTCAE v.4.03) and for laboratory assessments that include biochemistry, hematology, urinalysis; special safety assessments that include the regular monitoring and recording of blood glucose, insulin, HbA1c, GH and IGF-1, thyroid and liver function tests, gallbladder examinations and ECGs. Concomitant medications/Significant nondrug therapies will be assessed from study enrollment until the safety follow-up.	
To evaluate the long term effect of pasireotide LAR on HRQoL and signs and symptoms of acromegaly, from baseline and week 36 to week 72	Change in scores as measured by AcroQoL, EQ-5D-5L and signs and symptoms of acromegaly from baseline to week 72 and from week 36 to week 72.	

4 Study design

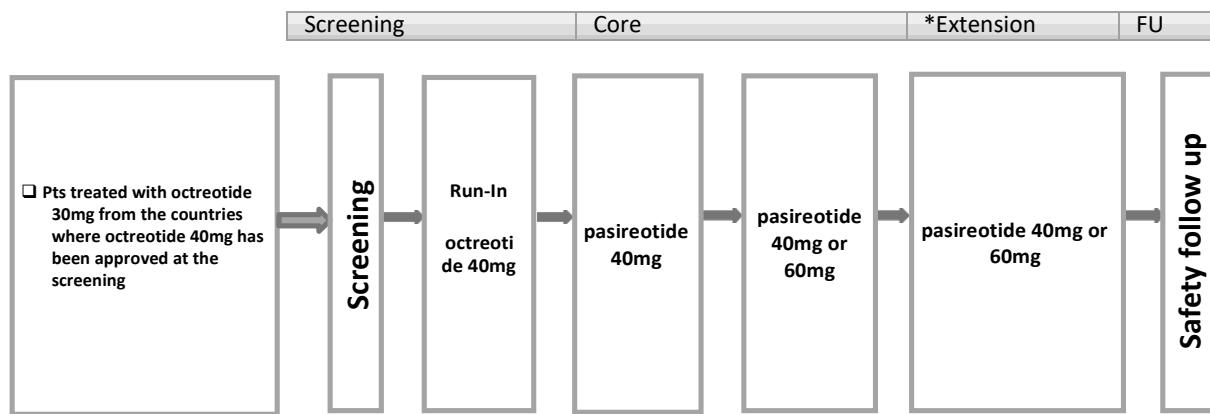
4.1 Description of study design

This is a phase IIIb multicenter, open-label; single arm study to evaluate the efficacy and safety of pasireotide LAR 40 mg and 60 mg in patients with inadequately controlled acromegaly with maximal doses of first generation somatostatin analogues. The study will enroll inadequately controlled patients by high doses of first -generation somatostatin analogues given for at least 3 months.

Figure 4-1 Flow Chart for Group 1 and Group 2 Patients



Group 1 – It consists of patients treated with octreotide LAR 30 mg from countries where octreotide LAR 40mg is approved for the treatment of acromegaly at the time of screening – These patients will start a run-in phase to receive 40mg octreotide before being considered eligible to enter the core treatment phase.

Figure 4-2 Study Design; Group 1

*Patients who do not achieve biochemical control at the end of the core phase (or at any time during the extension phase) will be allowed to use concomitant medications used to treat acromegaly based on the investigator's clinical judgment.

Run-In phase (Screening to Baseline)

Patients treated with octreotide LAR 30 mg who meet all inclusion criteria and no exclusion criteria will start treatment with octreotide LAR 40 mg in the run-in phase. Patients must have been treated with octreotide LAR 30 mg for at least three months before the screening visit. Patients will start treatment in the run-in phase and will receive octreotide LAR 40 mg every 4 weeks. After 3 months of treatment have been completed, and prior to the fourth injection (at visit 5), a mean GH and IGF-1 will be assessed.

Patients who are achieving biochemical control will be considered a screen failure and they will not qualify for the core phase of the study. They will continue treatment with octreotide LAR 40 mg outside the frame of this study.

Core Phase (Baseline to Visit 777)

Patients treated with octreotide LAR 40 mg in the run-in phase that meet all inclusion criteria and no exclusion criteria will be enrolled in the core phase of the study. The evaluation at the last visit of the run-in phase must be used for the eligibility assessment. Patients will start treatment with pasireotide LAR 40 mg every 4 weeks. At week 12, the mean GH value and IGF-1 value will be assessed. Patients who have not achieved biochemical control by week 12 and do not have any tolerability issues with pasireotide LAR 40 mg will have the dose increased to 60 mg. Patients who have achieved biochemical control by week 12 will maintain a dose of pasireotide LAR 40 mg. A mean GH value and IGF-1 value will be assessed every 12 weeks until Visit 777. At weeks 16 and 28, the investigator will be able to adjust the dose based on the achievement of biochemical control and drug tolerability. If tolerability issues occur, the dose can be decreased in 20 mg. Once the tolerability issue resolves, the patients should return to the dose previously received. Patients will be treated for a total of 36 weeks during the core phase. During this period any concomitant medication for the treatment of acromegaly is prohibited. Patients are required to complete a core phase completion visit 4 weeks after the last dose of pasireotide LAR is administered. Patients who discontinue from

the core phase are also required to complete the core phase completion visit 4 weeks after receiving the last pasireotide LAR dose.

Extension Phase (Visit 18 to Visit 778)

Patients who have completed all visits of core phase and have completed all the assessments at the core phase completion visit (Visit 777) can move into the extension phase. The core phase completion visit performed at Visit 777, will also be the first visit (Visit 18) of the extension phase. At Visit 18, the patients will receive the same dose of pasireotide LAR that they received at week 32 (Visit 17). At week 40 (Visit 19), the investigator will decide the treatment regimen and the pasireotide LAR dose based on the achievement of biochemical control at Visit 777. Patients achieving biochemical control at the end of the core phase will continue pasireotide LAR monotherapy at the same dose of the core phase. Patients who are uncontrolled at the end of the core phase will continue pasireotide LAR 60 mg and they will be allowed to receive concomitant treatment with medications used to treat acromegaly based on the investigator's clinical judgment. GH and IGF-1 levels will be assessed every 12 weeks until week 72. At weeks 52 and 64, the investigator will be able to adjust the dose of pasireotide LAR and the regimen of the concomitant medication used to acromegaly based on the patients achievement of biochemical control and drug tolerability. Patients will be treated for a total of 32 weeks in the extension phase and receive the last dose of study treatment at week 68 (Visit 26). Patients are required to complete an extension phase completion visit (Visit 778) 4 weeks after the last dose of pasireotide LAR is administered. Patients who prematurely discontinue from the extension phase are also required to complete the extension phase completion visit (Visit 778) 4 weeks after receiving the last dose of pasireotide LAR.

Safety follow-up

After discontinuation from the study or completion of study treatment either at the core phase or extension phase of the study, all patients will be followed for safety for 12 weeks (84 days) after the last study drug administration. This visit can be performed by phone, a study visit for follow-up is not mandatory.

Group 2 – It consists of patients treated with octreotide LAR 30 mg from countries where octreotide 40mg is NOT yet approved at the time of screening. This group also include patients already treated with octreotide LAR 40 mg or lanreotide ATG 120 mg. Patients should have been treated with the first generation SSAs for at least 3 months prior to screening. Eligible patients can directly enter the core treatment phase of the study. –A run-in phase is not required for this patient population.

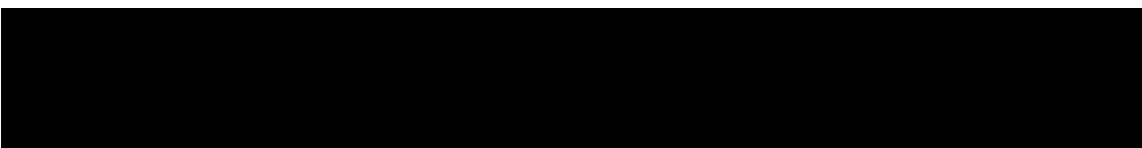
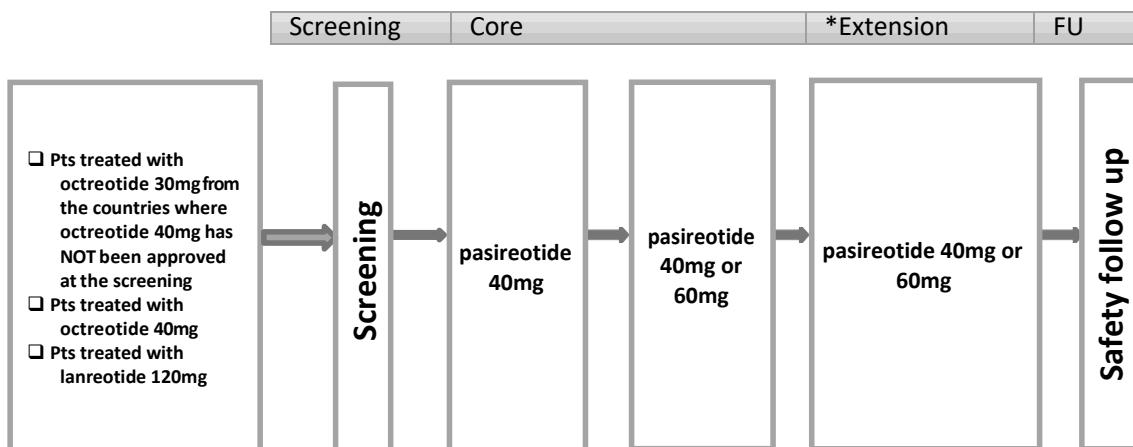


Figure 4-3 Study Design; Group 2

* Patients who do not achieve biochemical control at the end of the core phase (or at any time during the extension phase) will be allowed to use concomitant medications used to treat acromegaly based on the investigator's clinical judgment.

Core Phase (Baseline to Visit 777)

Please refer to the core phase for Group 1.

Extension Phase (Visit 18 to Visit 778)

Please refer to the extension phase for Group 1.

Safety follow-up

Please refer to Safety follow-up for Group 1.

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 will occur when all patients have completed their study completion visit and the follow up visit as per [Table 7-1](#) and [Table 7-2](#) (core phase) and [Table 7-3](#) (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 7.1.5](#) for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5 Population

5.1 Patient population

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

5.2 Inclusion criteria

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

1. Written informed consent must be obtained prior to any screening procedures
2. Male and female patients ≥ 18 years of age
3. Patients with confirmed diagnosis of inadequately controlled acromegaly as evidenced by the following:
 - A mean GH concentration of a 5-point profile over a 2-hour period $\geq 1 \mu\text{g/L}$ and sex- and age-adjusted IGF-1 $>1.3 \times \text{ULN}$
4. Patients treated with high dose of octreotide LAR (30 mg or 40 mg) or lanreotide ATG (120 mg) given as monotherapy for at least 3 months prior to screening (Visit 1)
 - Note: Patients currently being treated with octreotide LAR 30 mg from countries where the octreotide LAR 40 mg dose is approved at the time of screening will start a run-in phase in which they will receive the 3 injections of octreotide LAR 40 mg before being evaluated for eligibility for the core phase of the study

5.3 Exclusion criteria

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

1. Concomitant treatment with other medications known to reduce GH and or IGF-1, other than octreotide LAR or lanreotide ATG, unless discontinued 3 months prior to visit 1 (screening)
2. Patients with compression of the optic chiasm causing any visual field defect that requires surgical intervention
3. Diabetic patients with poor glycaemic control as evidenced by HbA1c $>8\%$ at Visit 1 for Group 2 and at both Visit 1 and Visit 5 for Group 1
4. Patients who are hypothyroid and not on adequate replacement therapy
5. Patients with symptomatic cholelithiasis and acute or chronic pancreatitis
6. Patients with clinically significant valvular disease
7. Patients with risk factors for torsade de pointes, i.e. patients with a baseline QTcF >450 ms in males, and >460 ms in females
8. Hypokalaemia, hypomagnesaemia, uncontrolled hypothyroidism, family history of long QT syndrome or concomitant medications with known risk of Torsades de pointes (TdP). Drugs with possible risk of TdP should be avoided whenever feasible.
9. Patients who have congestive heart failure (NYHA Class III or IV), unstable angina, sustained ventricular tachycardia, clinically significant bradycardia, advanced heart block, history of acute MI less than one year prior to study entry or clinically significant impairment in cardiovascular function

10. Concomitant disease(s) that could prolong the QT interval such as autonomic neuropathy (caused by diabetes or Parkinson's disease), HIV, cirrhosis, uncontrolled hypothyroidism or cardiac failure
11. Patients with liver disease such as cirrhosis, chronic active hepatitis, or chronic persistent hepatitis, or patients with ALT/AST > 2.0 X ULN, serum bilirubin >2.0 X ULN
12. Presence of Hepatitis B surface antigen (HbsAg) or Hepatitis C antibody test (anti-HCV)
13. Patients with serum creatinine >2.0 X ULN
14. Patients with WBC <3 X 10⁹/L; Hb 90% < LLN; PLT <100 X 10⁹/L
15. Patients with the presence of active or suspected acute or chronic uncontrolled infection
16. Patients who have undergone major surgery/surgical therapy for any cause within 4 weeks prior to visit 1 (screening)
17. Patients with active malignant disease within the last five years (with the exception of basal cell carcinoma or carcinoma in situ of the cervix)
18. 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)
19. History of syncope or family history of idiopathic sudden death
20. History of immunocompromise, including a positive HIV test result (ELISA and Western blot). A HIV test will not be required; however, previous medical history will be reviewed
21. Known hypersensitivity to somatostatin analogues or any other component of the pasireotide LAR
22. Patients who have a history of alcohol or drug abuse in the 6 month period prior to receiving pasireotide
23. Patients who have given a blood donation (of 400 ml or more) within 2 months before receiving pasireotide
24. Patients who have participated in any clinical investigation with an investigational drug within 1 month prior to dosing
25. Patients with any current or prior medical condition that, in the judgment of the investigator may interfere with the conduct of the study or the evaluation of the study results
26. 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
27. Sexually active males unless they use a condom during intercourse while taking drug and for 3 months following last dose of pasireotide 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.
28. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test
29. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and 3 months following last dose of pasireotide. Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception)
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 months prior to screening). For female subjects on the study the vasectomized male partner should be the sole partner for that subject
- Combination of any two of the following (a+b or a+c, or b+c):
 - a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
 - b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
 - c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

6 Treatment

6.1 Study treatment

Pasireotide LAR 40 mg or 60 mg will be administered as intra-muscular (i.m.) injections every 4 weeks for the core and the extension phases of the study. Patients will begin their treatment with pasireotide LAR 40mg every 4 weeks. Dose down-titration are permitted for patients who do not tolerate the protocol-specified dosing schedule. These dose adjustments are permitted in order to allow the patient to continue the study treatment. If tolerability issues occur, the dose is permitted to decrease by 20 mg. Please refer to [Section 6.2.1](#) for further instructions of dose adjustments. Octreotide LAR 40mg will be administered as intra-muscular injections every 4 weeks for the run-in phase if it applies. Dose up-titration of pasireotide LAR to 60 mg will be allowed after 12 weeks of treatment (i.e. after 3 injections) in patients who do not achieve adequate biochemical control and the 40mg is well tolerated. Prior to dose escalation it is recommended that glucose homeostasis is adequately controlled and that patients with HbA1c >8% should not have the dose of the pasireotide LAR increased to 60 mg.

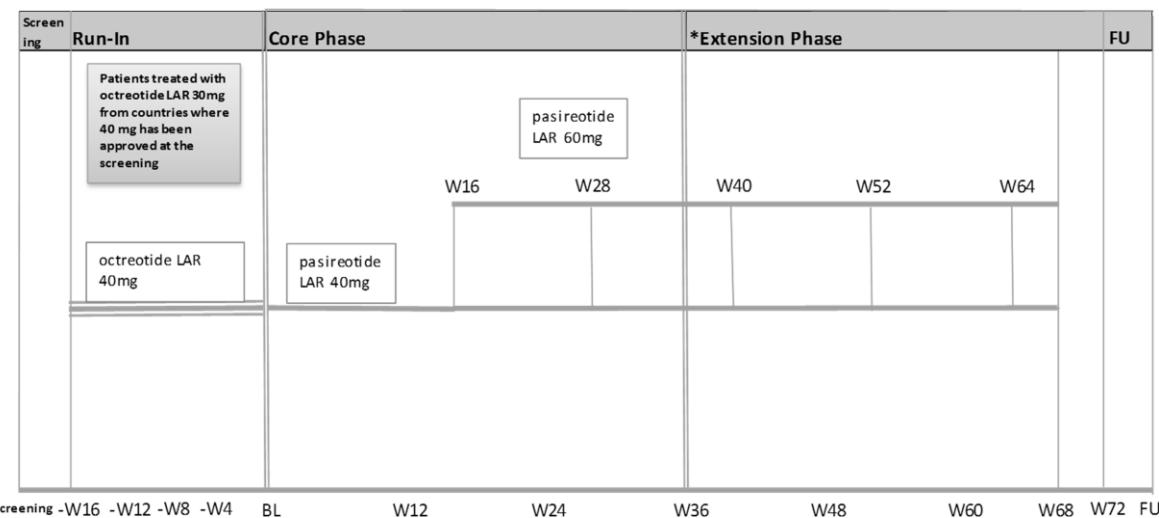
6.1.1 Dosing regimen

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
Pasireotide LAR	intra-muscular	10mg, 20mg, 40mg, 60 mg	every 4 weeks
Octreotide LAR	intra-muscular	40mg	every 4 weeks

Group 1 – Dosing Regimen

Figure 6-1 Group 1: Dose Regimen



* Patients who do not achieve biochemical control at the end of the core phase (or at any time during the extension phase) will be allowed to use concomitant medications used to treat acromegaly based on the investigator's clinical judgment.

Group 2 – Dosing Regimen

Figure 6-2 Group 2: Dose Regimen

* Patients who do not achieve biochemical control at the end of the core phase (or at any time during the extension phase) will be allowed to use concomitant medications used to treat acromegaly based on the investigator's clinical judgment.

6.1.2 Ancillary treatments

Not applicable.

6.1.3 **Rescue medication**

Not applicable.

6.1.4 Guidelines for continuation of treatment

For guidelines for continuation of treatment, refer to [Section 6.2 Dosing modification](#).

6.1.5 Treatment duration

Run-in Phase (Group 1 only)

Patients in this group will receive octreotide LAR 40 mg for 16 weeks in total. After the third month, biochemical control will be assessed for the eligibility criteria.

Core phase

Patients will continue to receive pasireotide LAR 40 mg or 60 mg until week 36, when all assessments will be done(Visit 18), receiving the last injection for the core phase at week 32 (Visit17).

Extension phase

At the end of the core phase, patients will have the option to continue study treatment with pasireotide LAR until week 68 (Visit 26). Patients who are not biochemically controlled during the extension will be allowed to receive concomitant treatment with medications used to treat acromegaly.

Patients can continue with study treatment until pasireotide LAR is commercially available and reimbursed in their respective country or until 68 weeks whichever occurs first. If pasireotide LAR is not commercially available and reimbursed and the patient is still receiving clinical benefit at 68 weeks as assessed by the investigator, the patient will have the opportunity to receive pasireotide LAR via a roll over study or a local access program if available.

6.1.6 Dose escalation guidelines

Not applicable.

6.2 Dose modifications

6.2.1 Dose modification and dose delay

Patients will begin their treatment with pasireotide LAR 40 mg every 4 weeks. Dose up-titration of pasireotide LAR to 60 mg will be allowed after 12 weeks of treatment (i.e. after 3 injections) in patients who do not achieve adequate biochemical control and the 40 mg is well tolerated. Prior to dose escalation it is recommended that glucose homeostasis is adequately controlled and that patients with HbA1c >8% should not have the dose of the pasireotide LAR increased to 60 mg.

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. If tolerability issues occur, the dose is permitted to decrease by 20 mg. Once the tolerability issue resolves, the dose should be returned to the one prior to the dose reduction. For guidance refer to [Table 6-2](#).

Down titrations of pasireotide LAR (from 60 mg to 40 mg, from 40 mg to 20 mg and from 20 mg to 10 mg) are permitted for patients with IGF-1 values that fall below the lower limit of normal and have controlled mean GH levels. The IGF-I values are required to be confirmed to be below LLN on two consecutive assessments; when IGF-I is found to be decreased to < LLN, a repeat measurement will be performed at the following visit for confirmation purposes. If biochemical control is maintained, the patient can continue on the lower dose for the remainder of the trial. If biochemical control is lost, the dose should be increased to the immediate previous dose administered.

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

LAR treatment	Adverse event	Action
Pasireotide LAR i.m.	AE CTC grade \leq 2	No drug adjustments
	AE CTC grade \geq 3 and assessed as study drug related	Reduce pasireotide LAR i.m. dose by 20 mg If the AE improves to grade \leq 2 before the next administration, increase dose back to the prior dose. If the dose is increased and the AE recurs at a grade \geq 3, the dose should be reduced again. The patient should stay on this lower dose if clinical benefits are maintained. No further dose titrations are allowed. If the AE does not improve to grade \leq 2, the dose is to be reduced further if clinical benefits are maintained. If the AE does not improve to grade \leq 2 on the minimum study dose, the treatment should be stopped. The patient should be discontinued and followed up for safety.

For the management of hyperglycemia, QT prolongation and LFT increases refer to specific instructions provided in [Section 6.2.2.3](#), [Section 6.2.2.1](#), and [Section 6.2.2.2](#).

For guidance on dosing modifications and safety reporting for octreotide LAR refer to the summary of product characteristics (SmPc).

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

6.2.2 Follow-up for toxicities

6.2.2.1 QT-prolongation

The results of the ECGs, cardiac examination and any recommendation provided by the cardiologist must be evaluated by the investigator to determine whether the patient should continue in the trial or not (discontinuation criteria to be followed).

6.2.2.1.1 $480 \text{ msec} < \text{QTcF} \leq 500 \text{ msec}$

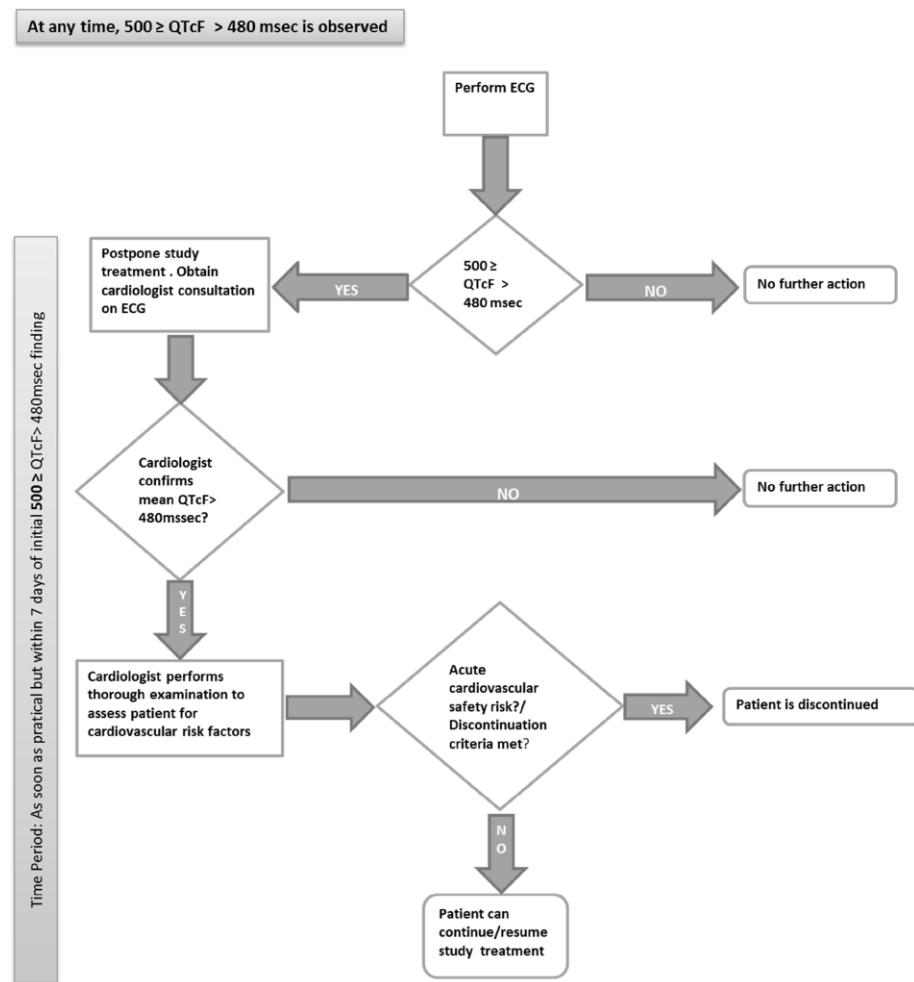
If at any visit a $480 \text{ msec} < \text{QTcF} \leq 500 \text{ msec}$ is observed for a first time for a patient at a given dose level, the following steps need to be taken (refer to [Figure 6-3](#)):

A cardiology consultation must be sought as soon as practical but within 7 days of the initial finding of abnormal ECG and the cardiologist must re-evaluate the ECG. The study treatment will be postponed until a cardiologist has re-evaluated the ECG.

- If a $\text{QTcF} > 480 \text{ msec}$ is NOT confirmed, no further action needs to be taken.
- If a $\text{QTcF} > 480 \text{ msec}$ is confirmed, a cardiologist must perform a thorough examination (such as reviewing baseline ECG, concurrent medications and performing a cardiovascular examination, including at least a cardiac auscultation) to assess the patient for cardiovascular risk factors.
 - If based upon the assessment by the cardiologist, the investigator considers that there is an acute cardiovascular safety risk and that the patient should not continue with study medication, the patient needs to be discontinued immediately (discontinuation criteria to be followed).

- If following the examination by the cardiologist, the investigator considers that there is no acute cardiovascular safety risk the patient could continue to receive study medication.

Figure 6-3 QT prolongation flowchart: 480 msec less than QTcF less than or equal to 500 msec

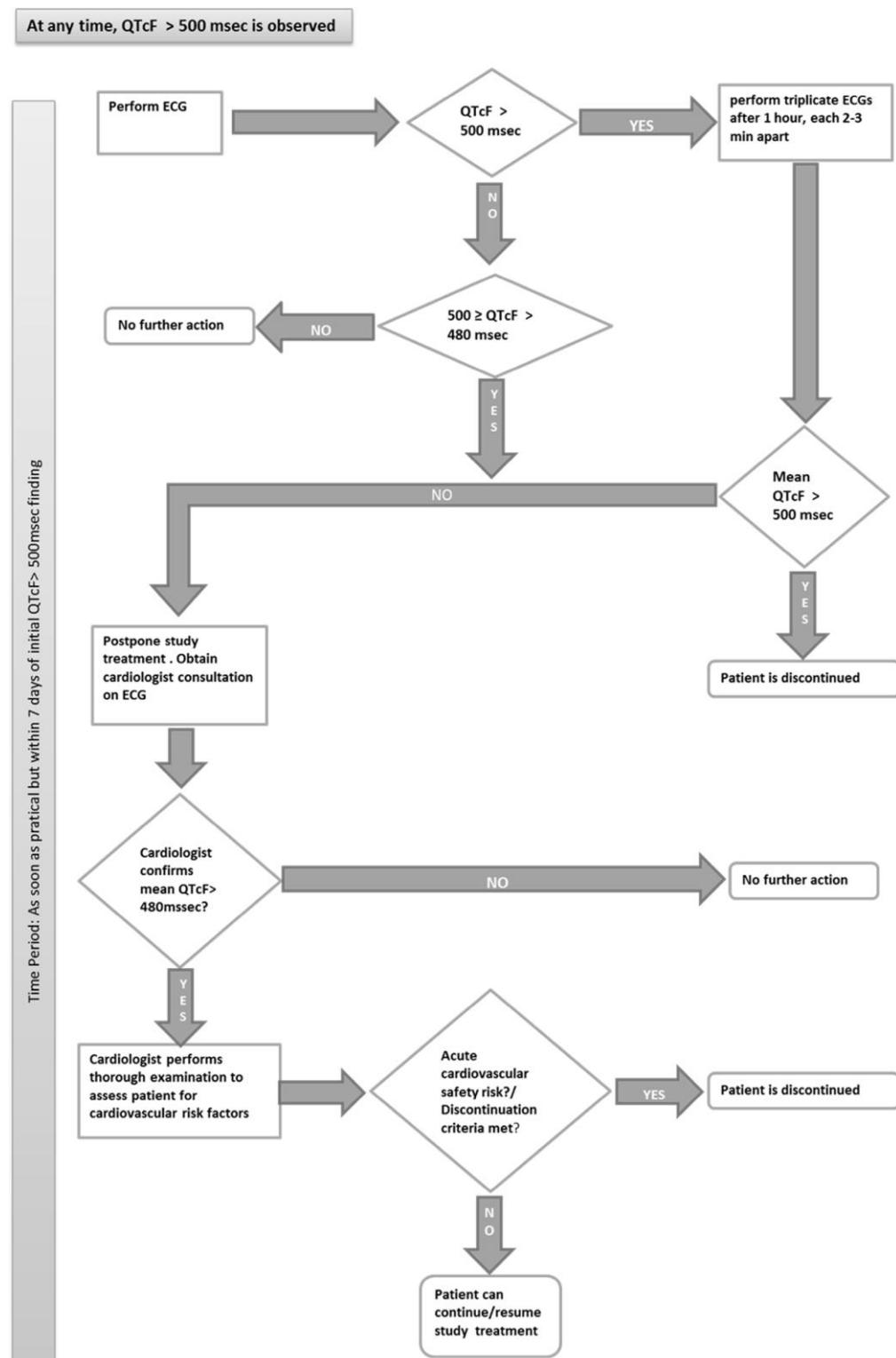


6.2.2.1.2 QTcF > 500msec

If at any visit a QTcF > 500msec is observed, the following steps need to be taken (refer to [Figure 6-4](#)):

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 > 500msec, the patient has to postpone study treatment until a cardiologist has re-evaluated the ECG. The re-evaluation needs to be done as soon as practical but within 7 days of the initial finding of abnormal ECG.

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

Figure 6-4 QT prolongation flowchart; QTcF greater than 500msec

6.2.2.2 Hepatic Safety management

Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding. If the finding is confirmed, the patient should be followed with frequent liver function monitoring until values return to pre-treatment levels.

If any of the criteria below are observed at any scheduled or unscheduled visit the sponsor should be notified immediately upon awareness and the hepatic safety follow up should be performed within **72 hours** of awareness of the abnormality:

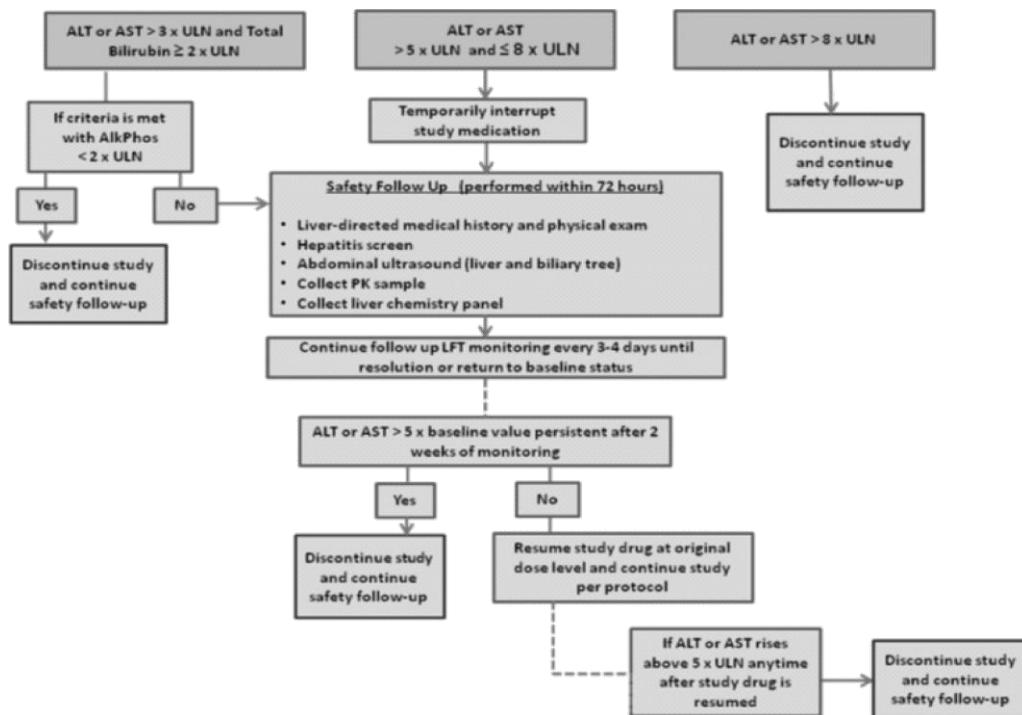
- ALT or AST $> 3 \times$ ULN and Total Bilirubin $\geq 2 \times$ ULN
- ALT or AST $> 5 \times$ ULN and $\leq 8 \times$ ULN
- ALT or AST $> 8 \times$ ULN

Hepatic Safety Follow up:

- Perform liver-directed medical history and physical examination (i.e. assess occupational hazards, concomitant medications including over-the-counter medications, inter-current illness, etc.)
- Liver chemistry tests: ALT, AST, total bilirubin, (fractionate to direct/indirect bilirubin if total bilirubin is $> 2.0 \times$ ULN), Albumin, PT (INR), ALP, and GGT. These tests should be monitored every **3-4 days** until resolution or return to baseline status.
- 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)

Patients should be managed according to the LFT algorithm [Figure 6-5](#) Patients may need to be discontinued if the abnormal liver function criteria are met upon LFT retesting or immediately discontinued without LFT retesting in the case of ALT or AST > 8 times the upper limit of normal (see discontinuation criteria [Section 7.1.5.1](#)). Progress reports of the event should be maintained until resolution or return to baseline status.

If any of these criteria are met and deemed an AE by the investigator, the event must be recorded on the Adverse Event CRF page; if the event is deemed serious by the investigator, then the SAE form should be completed. In addition, any clinically significant findings from the physical examination should be recorded on the Adverse Event CRF page.

Figure 6-5 LFT management algorithm

6.2.2.3 Hyperglycemia

Hyperglycemia is known to be associated with the treatment of somatostatin analogues (SSA). Clinical studies of pasireotide in healthy volunteers and in patients with Cushing's disease, acromegaly or carcinoid syndrome have reported transient, asymptomatic increases in fasting and postprandial glucose levels. Two clinical studies have been conducted [SOM230B2216] and [SOM230B2124] in healthy volunteers to further understand the mechanism of pasireotide-induced hyperglycemia and to evaluate the potential clinical utility of anti-diabetes agents in the management of pasireotide-induced hyperglycemia. Data from [SOM230B2216] study indicate that pasireotide decreases insulin secretion, particularly in the postprandial period, as well as the GLP-1/GIP secretion. Results from [SOM230B2124] study suggest that the incretin-based therapies (GLP-1 analogues and DPP-4 inhibitors) may have the best potential to manage the hyperglycemia associated with pasireotide. Some patients in [SOM230B2305], [SOM230C2305] and the [SOM230C2402] trials required insulin to treat their hyperglycemia.

Prior to dose escalation it is recommended that glucose homeostasis is adequately controlled and that patients with HbA1c >8% should not have the dose of the pasireotide LAR increased to 60 mg.

6.2.2.3.1 Self-monitoring of blood glucose

The principal investigator is to educate the patient on the signs and symptoms of hyperglycemia. Patients must monitor their fasting blood glucose by finger stick at home at least 3 times per week for the first 4-week treatment with pasireotide or when the dose of pasireotide is increased. If a patient does not have any fasting values above 100mg/dL,

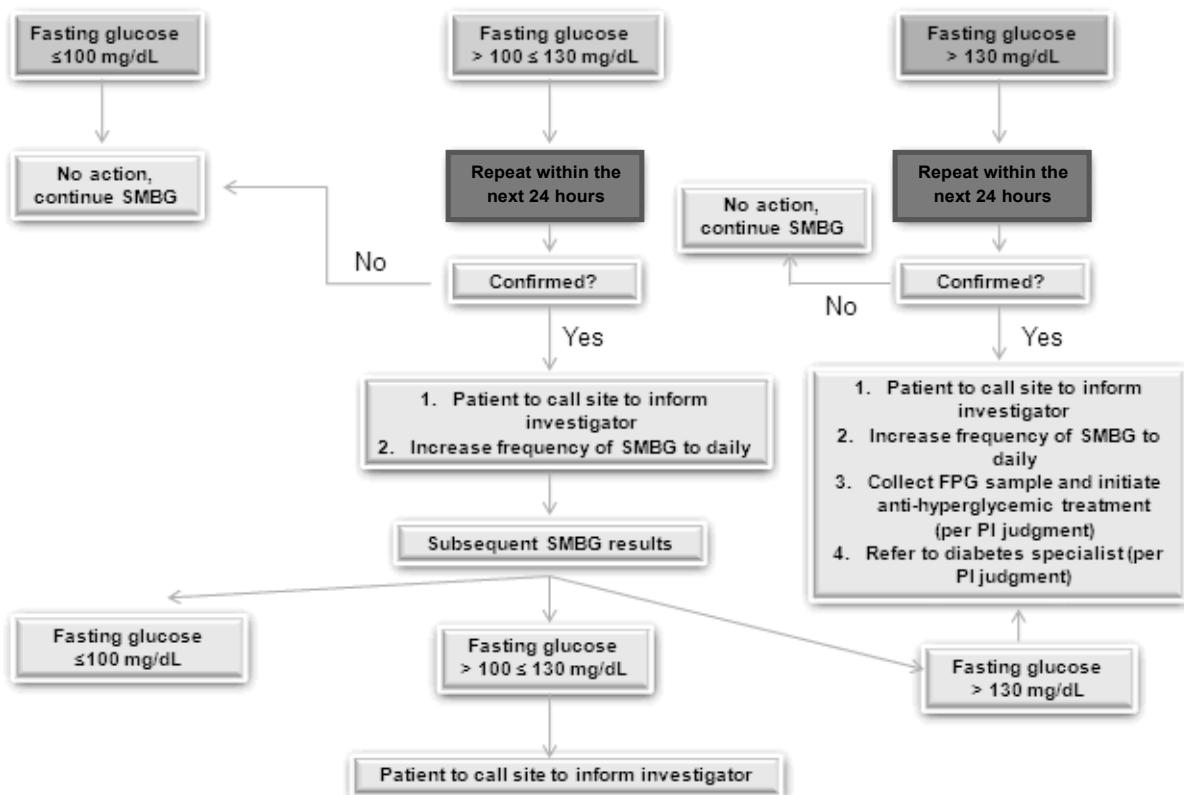
monitoring can be decreased to at least 2 times per week from week 4 to week 12 and 1 time every week for the rest of the study. If glucose values remain normal (below 100mg/dL), monitoring is at the investigator's discretion during the extension phase (where it is applicable). If any values are observed above 100mg/dL, the guidelines in [Figure 6-6](#) are to be followed. These guidelines are based on the current recommendations from the 2012 ADA and EASD aiming at a glycemic treatment goal of $FPG < 130\text{mg/dL} (< 7.2\text{mmol/L})$. 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 6-6](#). If fasting blood glucose values dictate initiation of anti-hyperglycemic treatment (i.e. confirmed $> 130\text{mg/dL}$ by self-monitoring), a fasting plasma glucose sample using the central laboratory is to be collected prior to initiation of anti-hyperglycemic treatment; however, treatment may be initiated using local laboratory results.

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

In addition to self-monitoring, fasting plasma glucose and HbA1c will be collected at study visits per [Table 7-1](#) to [Table 7-3](#). Close and frequent monitoring of blood glucose is needed during pasireotide treatment. Intervention for hyperglycemia is to be implemented in any patient meeting any of the following criteria: $FPG > 130\text{mg/dL}$ or $\text{HbA1c} \geq 6.5\%$.

Patients with $FPG > 160\text{mg/dL}$ or $\text{HbA1c} > 7.5\%$ 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 $> 250\text{mg/dL}$; $> 13.9\text{ mmol/L}$) at any point in the study should have the dose of pasireotide decreased. Patients who in spite of appropriate therapeutic interventions and despite dose reduction of study drug develop uncontrolled diabetes mellitus and/or consistently high blood glucose values: $FPG \geq 240\text{mg/dL}$ (13.3 mmol/L) or HbA1c value $\geq 10\%$ will require study treatment discontinuation.

Figure 6-6 Fasting SMBG Guidance

6.2.3 Anticipated risks and safety concerns of the study drug

Appropriate eligibility criteria, as well as specific dose modification and stopping rules are included in this protocol. Refer to [Section 7.1.5](#) for details.

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 increases are provided in [Section 6.2.2](#). Refer to preclinical toxicity and or clinical data found in the current [Investigator's Brochure].

6.3 Concomitant medications

6.3.1 Permitted concomitant therapy

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Concomitant Medications and Significant Non-Drug Therapies CRF. Diabetic patients must continue their treatment for diabetes throughout the study as indicated. If oral contraception is used, the patient must have been practicing this method of birth control for at least three months prior to enrollment and must agree to continue the oral contraceptive throughout the course of the study and for 12 weeks after the last dose of study drug.

6.3.1.1 Permitted concomitant therapy requiring caution and/or action

Acromegaly concomitant therapy is allowed only during the extension period for patients who do not achieve biochemical control. Otherwise, investigators should discourage patients from taking any medication during the study, with the exception of medications that are required to treat an adverse event.

In patients treated with medications that may decrease potassium levels (e.g. diuretics), more frequent monitoring of electrolytes is recommended as clinically indicated.

6.3.2 Prohibited concomitant therapy

The use of concomitant medication with a known risk of TdP is prohibited. In case a patient needs to take medication with a known risk of TdP, it will require study drug discontinuation prior to starting the medication. Please see [Appendix 3](#) for further guidance on medication with a known risk to TdP.

The following washouts are to be followed prior to screening

1. Dopamine agonists (bromocriptine, cabergoline) or pegvisomant (INN); 12 weeks
2. Pasireotide s.c.: 12 weeks
3. Pasireotide LAR: 12 weeks

6.4 Patient numbering, treatment assignment or randomization

6.4.1 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 Subject Number (Subject No.) consists of the Center Number (Center No.) (As assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form the patient is assigned to the next sequential Subject No. available to the investigator.

The investigator or designated staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. Once assigned, the Subject No. must not be reused for any other subject and the Subject No. for that individual must not be changed, even if the patient is re-screened. If the patient fails to be randomized or start treatment for any reason, the reason will be entered into the Screening Log. IRT must be notified within 2 days that the patient was not enrolled.

6.4.2 Treatment assignment or randomization

Prior to dosing, all patients who fulfill all inclusion/exclusion criteria will be assigned to pasireotide LAR 40 mg treatment arm. The investigator or his/her delegate will call or log on to the IRT and confirm that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a patient number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number but only for the pasireotide LAR treatment.

6.4.3 Treatment blinding

Not applicable.

6.5 Study drug preparation and dispensation

Detailed instructions on the use of pasireotide LAR for i.m. injection is provided in the pharmacy manual.

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug(s) will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

Pasireotide LAR will be provided as microparticles powder in vials containing nominally 20, 40 and 60 mg of Pasireotide (as free base) and solvent for suspension for injection in ampules for the reconstitution of the LAR microparticles.

Octreotide LAR 40 mg will be locally supplied to the site. The 40 mg dose is to be given as 2 separate injections (depending on dose availability at each country/site: either two injections of 20 mg each or a 30 mg and a 10 mg injection). Refer to the octreotide LAR package insert for further information.

6.5.1 Study drug packaging and labeling

The study medication packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the treatment arms and a [specific visit or dose/dose level]. Responsible site personnel will identify the study treatment package(s) to dispense to the patient by using the IRT and obtaining the medication number(s). Site personnel will add the patient number on the label. Immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique patient number.

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

Table 6-3 Packaging and labeling

Study treatments	Packaging	Labeling (and dosing frequency)
Pasireotide LAR	Microparticle powder for suspension in vial Solution for suspension (vehicle) in ampoule or pre-filled syringe	Labeled as 'SOM230' LAR (once/28days) Labeled as 'SOM230 Solvent' (once/28days)
Octreotide LAR	Octreotide LAR sourced locally	Octreotide LAR sourced locally

6.5.2 Drug supply and storage

Study drugs must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the study drugs should be stored

according to the instructions specified on the drug labels and in the current [Investigator's Brochure].

Table 6-4 Supply and storage of study treatments

Study treatments	Supply	Storage
Pasireotide LAR	Centrally or locally supplied by Novartis	Refer to study treatment label
Octreotide LAR	Octreotide LAR sourced locally	Refer to the label

6.5.3 Study drug compliance and accountability

6.5.3.1 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.

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

6.5.3.2 Study drug accountability

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

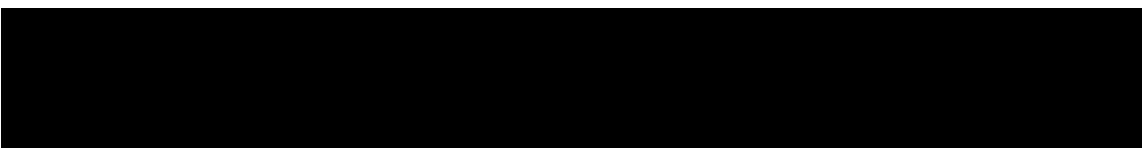
At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder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

6.5.3.3 Handling of other study treatment

Not applicable.

6.5.4 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 to Table 7-3 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. No CRF except Quality of Life Questionnaire will be used as a source document.

A \pm 2 day window will be permitted for the screening visit.

For all dosing visits, there is a general \pm 2 day window on assessments to take into account scheduling over public holidays. For all safety visits (visit without dosing), there is a general \pm 1 day window on assessments to take into account scheduling over public holidays.

Patients who discontinue treatment early must perform an end of core/extension phase visit 28 \pm 2 days from the last dose.

Table 7-1 Core Phase Visit evaluation schedule – Group 1

Table 7-2 Core Phase Visit evaluation schedule – Group 2

Table 7-3 Extension Phase Visit evaluation schedule for both Group 1 and Group 2

	Category	Protocol Section	18	19	20	21	22	23	24	25	26	778	Extension phase completion / discontinuation	Safety Follow Up	Study Evaluation Completion
Visit Number			18	19	20	21	22	23	24	25	26	778			779
Study Week			36	40	44	48	52	56	60	64	68		12 weeks after last study drug administration		
IRT Registration	D	7.1.2	x	x	x	x	x	x	x	x	x				
Patient history															
concomitant medications	D	7.1.2.3		x	x	x	x	x	x	x	x		x		
Physical examination	S	7.2.2.1				x			x				x		
Height	D	7.2.2.3											x		
Weight	D	7.2.2.3				x			x				x		
Vital signs	D	7.2.2.2		x	x	x	x	x	x	x	x		x		
Symptoms of acromegaly	D	7.2.1.2.3		x	x	x	x	x	x	x	x		x		
Laboratory assessments															
Hematology	D	7.2.2.4.1				x			x				x		
Clinical Chemistry (except LFT)	D	7.2.2.4.2				x			x				x		
LFT (ALT, AST, T-bil, Alb, ALP, γ -GT)	D	7.2.2.4.3				x			x				x		
Coagulation (APTT, PTT and PT(INR))	D	7.2.2.4.5				x			x				x		
5-point GH and IGF-1	D	7.2.1.1.1/7.2.1.1.2				x			x				x		
Fasting blood glucose	D	7.2.2.4.6		x	x	x	x	x	x	x	x		x		
HbA1c	D	7.2.2.4.6			x			x					x		
oGTT	D	7.2.2.4.6											x		

7.1.1 Molecular pre-screening

Not applicable.

7.1.2 Screening

The informed consent must be signed prior to ANY screening procedure being performed. The site should enter the IRT when a patient signs the informed consent and begins his/her screening. Patients that do not meet eligibility criteria are allowed to be rescreened and should use the same patient number. Rescreening should be documented in the source files. Should the cause of screening failure be normal GH and/or IGF-1, patients can be rescreened once these parameters go beyond the control level, the patient has continued to receive scheduled injection of the SSAs and had at least a 3-month treatment with maximal doses of first generation SSAs. Patient can only be re-screened a total of 2 times, and Novartis must be informed of the intent to re-screen a patient.

7.1.2.1 Eligibility screening

Following registration in the IRT for screening, patient eligibility will be checked once all screening procedures are completed. For Group 1 patients, patient eligibility will be checked again at the end of the run-in period prior to the baseline. The eligibility check will be embedded in the IRT system. Please refer and comply with detailed guidelines in the IRT Manual.

7.1.2.2 Information to be collected on screening failures

Patients who sign the informed consent, but fail to be started on study treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the applicable Screening Failure CRF pages. If the patient fails to be enrolled, the IRT must be notified within 2 days of the screen fail that the patient was not enrolled.

7.1.2.3 Patient demographics and other baseline characteristics

Standard demographic information and medical history will be collected. History of acromegaly, prior medications for acromegaly, AIP mutation and information on MRIs performed as standard of care will also be collected. Other baseline assessments will be collected as per [Table 7-1](#) and [Table 7-2](#).

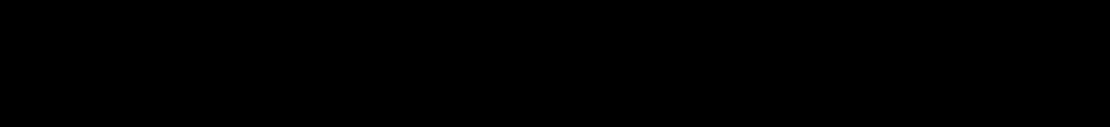
7.1.3 Run-in period

If a patient is considered as a Group 1, the run-in phase is required. Patients will be treated with octreotide LAR 40 mg for 16 weeks. The eligibility will be re-assessed after 3 months of octreotide LAR 40 mg.

7.1.4 Treatment period

Core Phase

Patients will be treated with pasireotide LAR until week 36, receiving the last core injection at week 32, unless they discontinue from the study treatment due to any reason. The core phase



completion visit is required at week 36. The safety follow up assessment is also required 56 days after the last study drug administration.

For details of assessments refer to [Table 7-1](#) and [Table 7-2](#).

Extension Phase

Patients will be treated with pasireotide LAR until 68 weeks, unless they discontinue from the study treatment due to any reason. Starting from week 40, acromegaly concomitant therapy is allowed for patients who do not achieve the biomedical control. The extension phase completion visit is required at week 72 (Visit 778). The safety follow up assessment is also required 56 days after the last study drug administration.

For details of assessments refer to [Table 7-3](#).

7.1.5 End of treatment visit including study completion and premature withdrawal

Patients who discontinue study treatment before visit 777 (week 36) in the core phase and visit 778 (week 72) in the extension phase, should be scheduled for a visit as soon as possible to have all assessments listed for the 777 or 778 visits performed ([Table 7-1](#) to [Table 7-3](#)). A Study Completion CRF page should be completed, giving the date and reason for stopping the study treatment. At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 56 days following the last dose of study treatment.

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

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

The investigator must contact IRT to register the patient's discontinuation.

For criteria for premature withdrawal refer to [Section 7.1.5.1](#).

7.1.5.1 Criteria for premature patient withdrawal

Patients may voluntarily withdraw from the study or be discontinued 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 values (s) and abnormal test procedures results (s)
- Patient withdrew consent
- Protocol deviation
- Physician decision
- Administrative problems

Patients must be withdrawn from the study in case of:

- Pregnancy
- Lost to follow up
- Death

In addition to the general withdrawal criteria, the study specific criteria below also require immediate study drug discontinuation. The safety follow-up management should be performed as outlined in [Section 6.2.2](#). Re-challenge of study medication is prohibited once discontinuation criteria are met.

Hepatic-related discontinuation criteria

- Jaundice or other signs of clinically significant liver dysfunction
- ALT or AST $> 3 \times$ ULN and Total Bilirubin $\geq 2 \times$ ULN and ALP $< 2 \times$ ULN
- ALT or AST $> 5 \times$ ULN $\leq 8 \times$ ULN persistent for more than 2 weeks
- ALT or AST $> 8 \times$ ULN

QT related discontinuation criteria

Patients experiencing adverse events in QTc:

- QTcF > 500 msec, if confirmed by a cardiologist.
- QTcF > 480 msec, if the investigator determines it is no longer safe for the patient to continue in the study, based on ECGs, cardiac examination and recommendation from a cardiologist.
- Clinically significant arrhythmias including:
 - Any ventricular or supra-ventricular tachyarrhythmia associated with symptoms of hemodynamic compromise.
 - Sustained ventricular tachycardia (>30 s) irrespective of symptoms.
 - Clinically significant brady-arrhythmia or third degree AV block.
- Need to use QT prolonging medication with known risks factors for torsade de pointes.

Hyperglycemia related discontinuation criteria

- Uncontrolled diabetes mellitus (DM), consistently high capillary glucose values in excess of 275 mg/dL (15.5 mmol/L), FPG \geq 240 mg/dL (13.3 mmol/L) or HbA1c value \geq 10 % despite prior appropriate management and prior dose adjustment of the study drug

The investigator must also notify the IRT of the premature withdrawal, if this occurs during the core period. Patients who withdraw prematurely from the core phase cannot participate in the extension phase.

7.1.6 Follow-up and End of Study visit

All patients must have safety evaluations and complete the safety follow up assessments at the 56 days after the last dose of pasireotide LAR.

Patients lost to follow up should be recorded as such on the CRF. For patients who are lost to follow-up, the investigator should show “due diligence” by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. Patients that meet the requirements for follow up of abnormal LFTs at the end of study visit should be followed up as detailed in [Section 6.2.2.2](#).

7.2 Assessment types**7.2.1 Efficacy assessments****7.2.1.1.1 GH (5-point mean GH level)**

A 5-point mean GH will be assessed from a 2-hour profile after one hour at rest at the hospital and prior to the study drug administration at week -20 (Group1 only), week -4, week 12, 24, 36 in the core phase and at week 48, 60, 72 in the extension phase.

The 5-point mean GH profile is to be done within a 2-hour time period prior to glucose intake when an oGTT is required.

All GH 2-hour profiles should be taken at the same time in the morning. The samples for GH will be analyzed by the central laboratory. Please refer to the central laboratory's [\[Clinical Trial Laboratory Manual\]](#) for processing details.

7.2.1.1.2 IGF-1

Total IGF-1 levels will be assessed at the same visits as GH with one pre-dose sample which is week -20 (Group1 only), week -4, week 12, 24, 36 in the core phase and at week 48, 60, 72 in the extension phase. Blood sampling for IGF-1 will be done prior to the study drug administration and glucose intake for oGTT when applicable. This sample must be taken together with the first sample of the GH profile. The samples for IGF-1 will be analyzed by the central laboratory. Please refer to the laboratory's [\[Clinical Trial Laboratory Manual\]](#) for processing details.

7.2.1.2 Secondary efficacy assessments

7.2.1.2.1 GH and IGF-1:

Both values in combination or alone will be used to assess secondary efficacy parameters at week 12, 24 and 36 in the core phase and at week 48, 60 and 72 in the extension phase.

7.2.1.2.2 Health-Related Quality of Life (HRQoL)

Patient Reported Outcomes Assessment:

HRQoL will be assessed at baseline, week 12, 24, visit 777(core phase completion) and at visit 778 (extension phase completion) using the AcroQoL, an acromegaly-specific quality of life instrument. The AcroQoL instrument is comprised of 22 questions divided into two scales: one evaluating physical aspects (8 items) and the other that addresses psychological aspects (14 items). The psychological scale can also be further divided into subscale that evaluates physical appearance and the other subscale focused on the impact of the disease on personal relationships of the patient (7 items each). Each of the questions has a 5-item Likert scale. The instrument was developed with input from both physicians and patients to assess those dimensions of health-related quality of life most relevant and bothersome to patients with this disease. It has been found to be a valid, reliable instrument, that is sensitive to changes in the concepts being measured ([Badia et al 2004](#)).

Health Status:

Health status will be measured at baseline and weeks 12, 24, visit 777 and visit 778 using the EQ-5D-5L, a valid and reliable instrument for measuring general health status. The EQ-5D-5L consists of 2 pages – the descriptive system and the EQ visual analogue scale (EQ VAS) ([Herdman M et al 2011](#)) The descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each with 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ VAS records the respondent's self-rated health on a 20 cm vertical, visual analogue scale with endpoints labeled 'the best health you can imagine' and 'the worst health you can imagine' Laboratory evaluations.

7.2.1.2.3 Symptoms of acromegaly

Symptom of acromegaly are to be collected at visits indicated in [Table 7-1](#) to [Table 7-3](#) and appropriate CRFs. Ring size will be measured with a gauge using 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 measurement will be provided on a scale of 1-15 including half sizes. The investigator will also ask the patient to score the following symptoms of acromegaly: headache, fatigue, perspiration, paresthesias, osteoarthralgia according to a five-point score scale (0=absent, 1=mild, 2=moderate, 3=severe, 4=very severe).

7.2.2 Safety and tolerability assessments

7.2.2.1 Physical examination

A complete physical examination must be performed by the investigator at visits indicated in [Table 7-1](#) to [Table 7-3](#). The examinations will be performed according to the standards at each institution.

Information about the physical examination must be present 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 Medical History/Current Medical Condition page on the patient's CRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's CRF.

7.2.2.2 Vital signs

Vital signs (supine blood pressure, supine pulse rate and body temperature) will be performed by the investigator at all visits as indicated in [Table 7-1](#) to [Table 7-3](#) and appropriate CRFs.

7.2.2.3 Height and weight

Height in centimeters and weight to the nearest 0.1 kilogram (in indoor clothing, but without shoes) are to be collected at visits indicated in [Table 7-1](#) to [Table 7-3](#) and appropriate CRFs.

7.2.2.4 Laboratory evaluations

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

Urinalysis and urine pregnancy test will be performed by dipstick locally. The dipsticks will be provided to the sites by the central laboratory.

Table 7-4 Local or Central Clinical Laboratory Parameters Collection Plan

Test Category	Test Name
Hematology (central)	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, RBC Morphology with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)
Clinical Chemistry (central)	Bicarbonate, Calcium, Chloride, Creatinine, Creatine Kinase, Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, α -amylase, Lipase, Lactic Dehydrogenase (LDH), Magnesium, Sodium, Potassium, Prolactin,
LFT (central)	ALT, AST, Total bilirubin, (total bilirubin should be differentiated into direct and indirect reacting bilirubin if total bilirubin is increased > 2.0 ULN), Albumin, ALP and GGT
Hepatic Screening (central)	HbsAg, AntiHCV
Hyperglycemia related test (central)	Fasting Blood Glucose, Glycosylated Hemoglobin (HbA1C), oGTT (insulin and plasma glucose)
Coagulation (central)	Prothrombin time (PT) or International normalized ratio (INR), Partial thromboplastin time (PTT), Activated partial thromboplastin time (APTT)

Test Category	Test Name
Thyroid and hormones (central)	T4 [free], TSH, Plasma Adrenocorticotropic Hormone (ACTH), Fasting Serum Cortisol,
Urinalysis (local)	Macroscopic Panel (Dipstick) (Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, pH, Protein, Specific Gravity)
Additional tests (central)	Insulin-like growth factor 1 (IGF-1), Growth Hormone (GH)
Pregnancy Test	Urine (dipstick) and serum B-hCG

7.2.2.4.1 Hematology

Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, RBC Morphology with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils) are to be collected at visits indicated in [Table 7-1](#) to [Table 7-3](#).

7.2.2.4.2 Clinical Chemistry

Bicarbonate, Calcium, Chloride, Creatinine, Creatine Kinase, Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, α -amylase, Lipase, Lactic Dehydrogenase (LDH), Magnesium, Sodium, Potassium, Prolactin are to be collected at visits indicated in [Table 7-1](#) to [Table 7-3](#).

7.2.2.4.3 Liver function testing (LFT)

ALT, AST, Total bilirubin, (total bilirubin should be differentiated into direct and indirect reacting bilirubin if total bilirubin is increased > 2.0 ULN), Albumin, ALP and GGT are to be collected at visits indicated in [Table 7-1](#) to [Table 7-3](#).

7.2.2.4.4 Hepatic Screening

HbsAg, AntiHCV are to be collected at visit 1.

7.2.2.4.5 Coagulation

Prothrombin time (PT) or International normalized ratio (INR), Partial thromboplastin time (PTT), Activated partial thromboplastin time (APTT) are to be collected at visits indicated in [Table 7-1](#) to [Table 7-3](#).

7.2.2.4.6 Hyperglycemia related test

Fasting Blood Glucose, Glycosylated Hemoglobin (HbA1C), oGTT (insulin and plasma glucose) are to be collected at visits indicated in [Table 7-1](#) to [Table 7-3](#). Diabetic patients are not required to perform oGTT. If the patient discontinues from the study, the oGTT at visit 777/778 can be performed based on the judgment of the investigator.

7.2.2.4.7 Thyroid and hormones

T4 (free), TSH, ACTH, Fasting Serum Cortisol are to be collected at visits indicated in [Table 7-1](#) to [Table 7-3](#).

7.2.2.4.8 Urinalysis

Dipstick measurements for Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, pH, Protein, Specific Gravity are to be collected at visits indicated in [Table 7-1](#) to [Table 7-3](#).

7.2.2.4.9 Pregnancy

All pre-menopausal women who are not surgically sterile will have a serum B-hCG pregnancy test at screening, baseline and end of treatment (visit 777 and visit 778) and urine pregnancy test at visits indicated in [Table 7-1](#) to [Table 7-3](#)

A positive pregnancy test by urine is required an immediate serum B-hCG pregnancy test.

A positive pregnancy test requires immediate interruption of study treatment until the assessment is confirmed. If positive, the patient must discontinued from the study.

7.2.2.5 Gallbladder ultrasound

Table 7-5 Gallbladder Ultrasound Assessment Collection Plan

Group 1

Procedure	Screening/Run-in/Baseline	During Treatment/Follow-up
Gallbladder Ultrasound	Mandated (Week -20 and Week -4)	Week 12, 24, Visit 777 (core phase) Week 60, Visit 778 (extension phase)

Group 2

Procedure	Screening/Baseline	During Treatment/Follow-up
Gallbladder Ultrasound	Mandated (Week -4)	Week 12, 24, Visit 777(core phase) Week 60, Visit 778 (extension phase)

A gallbladder ultrasound will be performed at the sites at visits indicated in [Table 7-1](#) to [Table 7-3](#). The results will be recorded in the CRFs.

7.2.2.6 Cardiac assessments

7.2.2.6.1 Electrocardiogram (ECG)

Table 7-6 Central ECG Collection Plan

Group 1

Week	Time	ECG Type
-20 (Screening Run-In)	Pre-dose	12 Lead
-4 (Run-in)	Pre-dose	12 Lead
0 (Baseline)	Pre-dose	12 Lead
3	At any time during the visit	12 Lead
4	Pre-dose	12 Lead
7	At any time during the visit	12 Lead
8	Pre-dose	12 Lead
11	At any time during the visit	12 Lead

Week	Time	ECG Type
12	Pre-dose	12 Lead
Every 4 weeks until Visit 777 (core phase), until week Visit 778 (extension phase)	Pre-dose	12 Lead
Unscheduled visit	As clinically indicated	12 Lead

Group 2

Week	Time	ECG Type
-4 (Screening)	Pre-dose	12 Lead
0 (Baseline)	Pre-dose	12 Lead
3	At any time during the visit	12 Lead
4	Pre-dose	12 Lead
7	At any time during the visit	12 Lead
8	Pre-dose	12 Lead
11	At any time during the visit	12 Lead
12	Pre-dose	12 Lead
Every 4 weeks until Visit 777 (core phase), until Visit 778 (extension phase)	Pre-dose	12 Lead
Unscheduled visit	As clinically indicated	12 Lead

Standard 12 lead ECGs will be performed at the sites at visits indicated in [Table 7-1](#) to [Table 7-3](#).

If at any visit QTcF >480 msec is observed, all the procedures for QT-prolongation described in [Section 6.2.2.1](#) should be followed.

Interpretation of the tracing must be made by a qualified physician and documented on the ECG CRF page. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities present when the patient signed informed consent should be reported on the Medical History CRF. Clinically significant findings must be discussed with Novartis prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events CRF.

Each ECG should be taken prior to the study drug administration. At the discontinuation (including the core phase completion visit for patients who do not participate in the extension phase) or the extension phase completion visit, the ECG should be taken prior to the commercial drug administration.

7.2.2.6.2 Cardiac imaging - MUGA (multiple gated acquisition) scan or echocardiogram

Not applicable.

7.2.2.6.3 Cardiac enzymes

Not applicable.

7.2.2.7 Tolerability

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

7.2.3 Pharmacokinetics

Not applicable.

7.2.3.1 Other assessments

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

7.2.4 Resource utilization

Not applicable.

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Except for screening failures, adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Relevant Medical History/Current Medical Conditions CRF. Adverse event monitoring should be continued for at least 12 weeks following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate adverse event.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

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

The occurrence of adverse events should be sought by non-directive questioning of the patient during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during the

screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade
2. Its duration
3. Its relationship to the study treatment
4. Action taken with respect to study or investigational treatment
5. Whether medication or therapy was given
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 CRF.

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

8.1.2 Laboratory test abnormalities

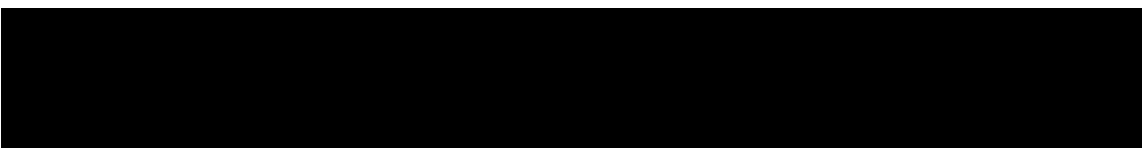
8.1.2.1 Definitions and reporting

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

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

8.1.3 Adverse events of special interest

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



The current list of adverse events of special interest is provided below; this list is not all inclusive and can be modified throughout the lifetime of the trial:

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

8.2 Serious adverse events

8.2.1 Definitions

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

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
 - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition

- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

8.2.2 Reporting

To ensure patient safety every SAE regardless of suspected occurring after the patient has provided informed consent and until 12 weeks (84 days) after the patient has stopped study drug administration must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after the 12 weeks (84 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 in English, and send the completed, signed form by fax within 24 hours to the oncology Novartis Drug Safety and Epidemiology (DS&E) department.

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

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

If the SAE is not present in the Reference Safety Information section of the [Investigator's Brochure] (unexpected) and is thought to be related to the Novartis study treatment (suspected), an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Suspected Unexpected Serious Adverse Reactions 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. 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.

8.3 Emergency unblinding of treatment assignment

Not applicable.

8.4 Pregnancies

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

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

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.

Newborn of a patient (or a partner of a patient) who becomes pregnant during the study treatment or within 3 months after the last pasireotide LAR dose should be followed for 3 months post-delivery (from Day 0 to Month 3 of life).

8.5 Warnings and precautions

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

8.6 Data Monitoring Committee

No Data Monitoring Committee is planned for this trial.

8.7 Steering Committee

A steering committee (SC) will be established comprising investigators participating in the trial, i.e. not being Novartis representatives from the Clinical Trial Team.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team the SC will also



develop recommendations for publications of study results including authorship rules. The details of the role of the SC will be defined in a SC charter.

9 Data collection and management

9.1 Data confidentiality

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

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

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

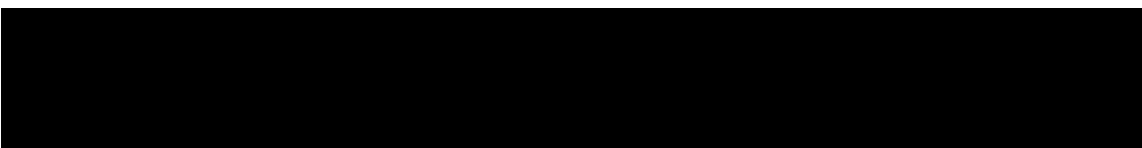
The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification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

9.2 Site monitoring

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

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and



documentation of SAEs. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

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.

9.3.1 ECG data collection

ECG data will be collected via 12-lead digital ECG machines. The data will be transmitted to an ECG vendor for centralized cardiac safety analysis, as well as further processing and data reconciliation.

9.3.2 IRT data collection

Patient eligibility and enrollment will be tracked using an Interactive Response Technology. The system will be supplied by a vendor, who will also manage the database for that system.

9.3.3 Central laboratory data collection

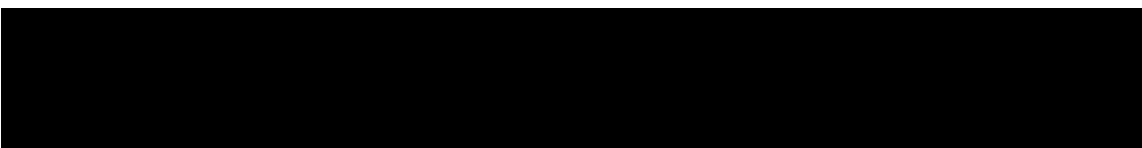
All laboratory evaluation except urinalysis and urine pregnancy test will be conducted and its data will be collected by the central laboratory.

Designated investigator staff must enter the sample information required by the protocol onto sample collection eCRFs, as well as central laboratory requisition forms. The requisition forms will be printed on 2-part, non-carbon-required paper or will available electronically. If paper forms will be used, one copy of the requisition form will be forwarded to the central laboratory along with the corresponding sample(s), and the other will be retained by the site. CRA will review the central laboratory requisition forms against the sample collection eCRFs for completeness and accuracy, and instruct site personnel to make any required corrections or additions. Further reconciliation of any sample collection data that were collected on both eCRFs and requisition forms will be performed by the designated central laboratory and Novartis.

The samples will be shipped by the site to a designated central laboratory for sample management.

9.4 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the



investigational site via the EDC system. Designated investigator and 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).

Patient numbers and data about all study treatments dispensed to the patient and all IRT assigned dosage changes will be tracked using an Interactive Response Technology. The system will be supplied by a vendor(s), who will also manage the database. The data will be sent electronically to Novartis personnel (or designated CRO).

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

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

10 Statistical methods and data analysis

This is a phase IIIb exploratory study to assess the efficacy and safety of pasireotide in patients with acromegaly inadequately controlled with first generation somatostatin analogues. The data will be analyzed by Novartis and/or designed CRO. It is planned that the data from all centers that participate in this protocol will be used. Continuous variables will be summarized by number of patients, mean, standard deviation, minimum, 25th quantile, median, 75th quantile and maximum. Categorical variables will be summarized by absolute and relative frequencies. Unless otherwise stated, baseline assessment refers to the last assessment prior to the patient's first study drug dose recorded after the signing of the informed consent.

10.1 Analysis sets

10.1.1 Full Analysis Set

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

10.1.2 Safety Set

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

10.1.3 Per-Protocol Set

The Per-Protocol Set (PPS) consists of a subset of the patients in the FAS who are compliant with requirements of the CSP. The protocol deviations criteria will be defined prior to database lock.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data (e.g. age, gender, race, GH levels, standardized IGF-1 levels) will be summarized descriptively for the FAS.

10.3 Treatments (study treatment, concomitant therapies, compliance)

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

These analyses will be performed on the safety set.

10.4 Primary objective

To evaluate the efficacy of pasireotide LAR in patients with acromegaly who are inadequately controlled with currently available somatostatin analogues, as measured by the proportion of patients with GH <1 μ g/L and IGF-1 <ULN at week 36.

10.4.1 Variable

The variable of interest is proportion of patients who achieved GH <1 μ g/L and IGF-1 <ULN at week 36.

10.4.2 Statistical hypothesis, model, and method of analysis

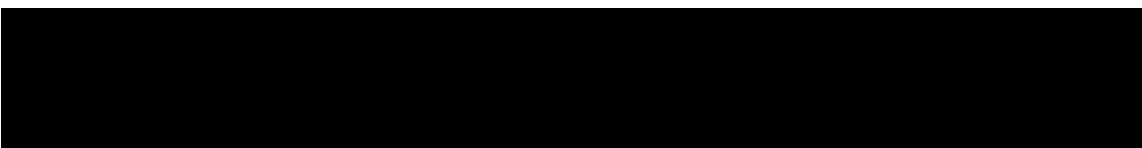
The trial is exploratory in nature and no formal hypothesis testing is planned.

The proportion of patients achieving mean GH levels < 1 μ g/L and IGF-1 <ULN will be calculated along with its two-sided, asymptotic or exact when the criteria for asymptotic approximation were not fulfilled, 95% confidence interval at Week 36.

10.4.3 Handling of missing values/censoring/discontinuations

If a patient has less than three samples for the assessment of the 5-point mean GH from the 2-hour profile, then the mean GH will be considered as missing. Patients with missing GH and or IGF-1 assessment at week 36 will be considered as non-responders.

Multiple imputation method or other adequate methods will be employed to impute missing data and sensitivity analyses will be performed using imputed missing data to assess the robustness of the efficacy findings. The imputation methods as well as sensitivity analyses will be specified in the RAP.



10.4.4 Supporting Analysis of Primary Objective

To assess the proportion of patients achieving GH <1 µg/L and IGF-1 <ULN at weeks 36 by sub-groups of GH level at screening

The proportion of patients who achieved GH <1µg/L and IGF-1 <ULN at week 36 among two sub-groups of patients, those having GH level at screening between 1µg/L and 2.5µg/L, and those having GH level >2.5µg/L at screening, will be reported along with their two-sided (exact or asymptotic, depending on assumptions being satisfied) 95% confidence interval.

These supporting analyses is purely exploratory in nature and no statistical multiplicity adjustments will be performed to distinguish it from other endpoints.

10.5 Secondary objectives

The secondary efficacy analysis will be performed on the FAS. The same rule of handling missing values for GH and IGF-1 variables as specified in the analysis of the primary efficacy variable will be used.

10.5.1 Secondary objectives- Core phase

To assess the changes in mean GH from study baseline to week 36

Descriptive summaries of actual and percentage change in GH from study baseline to week 36 values will be provided.

To assess the changes in standardized IGF-1 from study baseline to week 36

Descriptive summaries of actual and percentage change in standardized IGF-1 from study baseline to week 36 values will be provided.

To assess the proportion of patients achieving GH <1 µg/L and IGF-1 <ULN at weeks 12 and 24 overall and by GH level at screening

Proportion of patients who achieved GH <1µg/L and IGF-1 <ULN at week 12 and 24 will be reported along with its corresponding 95% confidence interval for all patients and also among patients, having GH level at screening between 1 µg/L and 2.5 µg/L, and among patients having GH level at screening > 2.5 µg/L.

To assess the proportion of patients achieving GH <1µg/L at weeks 12, 24 and 36, overall and by GH level at screening

Proportion of patients who achieved GH <1µg/L at week 12, 24 and 36 will be reported along with its corresponding 95% confidence interval for all patients and also among patients, having GH level at screening between 1 µg/L and 2.5 µg/L, and patients having GH level at screening >2.5 µg/L.

To assess the proportion of patients achieving IGF-1 levels <ULN at weeks 12, 24 and 36

Proportion of patients who achieved IGF-1 <ULN at week 12, 24 and 36 will be reported along with its corresponding 95% confidence interval.

To evaluate the effect of pasireotide LAR on HRQoL and signs and symptoms of acromegaly from baseline to weeks 12, 24 and 36

Descriptive statistics, including mean, median, standard deviation, minimum and maximum, will be presented to describe actual standardized scores as measured by HRQoL and changes from baseline to weeks 12, 24 and 36.

For each of the acromegaly symptoms (ring size, headache, fatigue, perspiration, paresthesias, osteoarthralgia), descriptive summaries of actual and changes from baseline to weeks 12, 24 and 36 will be provided. Moreover, shift tables from baseline to the most extreme post-baseline value will also be presented for acromegaly symptoms except ring size

To evaluate the tolerability and safety profile of pasireotide LAR

Same analysis as in [Section 10.5.3](#)

10.5.2 Secondary objectives- Extension phase

To assess the proportion of patients achieving IGF-1 <ULN at weeks 48, 60 and 72

Proportion of patients who achieved IGF-1 <ULN will be calculated along with its two-sided 95% confidence interval at week 48, 60 and 72.

To assess the proportion of patients achieving GH<1 µg/L and IGF-1<ULN at weeks 48, 60 and 72 by treatment with pasireotide LAR alone or with concomitant medications used to treat acromegaly

Proportion of patients who achieved GH<1µg/L and IGF-1<ULN by treatment with pasireotide LAR alone or with concomitant medications used to treat acromegaly will be reported separately along with its corresponding 95% confidence interval at weeks 48, 60 and 72

To assess the proportion of patients achieving GH <1 µg/L at weeks 48, 60 and 72 by treatment with pasireotide LAR alone or with concomitant medications used to treat acromegaly

Proportion of patients who achieved GH<1µg/L by treatment with pasireotide LAR alone or with concomitant medications used to treat acromegaly will be reported separately along with its corresponding 95% confidence interval at weeks 48, 60 and 72

To evaluate the long term effect of pasireotide LAR on HRQoL and signs and symptoms of acromegaly, from baseline and week 36 to week 72

Change in standardized scores as measured by HRQoL and signs and symptoms of acromegaly from baseline and week 36 to week 72.

Descriptive statistics, including mean, median, standard deviation, minimum and maximum, will be presented to describe actual standardized scores as measured by HRQoL and changes from baseline to week 72 and from week 36 to week 72.

For each of the acromegaly symptoms (ring size, headache, fatigue, perspiration, paresthesias, osteoarthralgia), descriptive summaries of actual and changes from baseline to weeks 72, and from week 36 to week 72 will be provided. Moreover, shift tables from baseline to the most extreme post-baseline value, and from week 36 to the most extreme value up to week 72 will also be presented for acromegaly symptoms except ring size.

To evaluate the long term tolerability and safety profile of pasireotide LAR

Same analysis as in [Section 10.5.4](#)

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.

For the core phase, all listings and tables will be presented overall and by maximum dose given. For AEs of special interest, tables will be presented by the given dose as well (AE starts or worsens while the patient is being treated at that dose level.)

For the extension phase, all listings and tables will be presented overall and by type of treatment (monotherapy, combination dopamine agonist, and combination with GH receptor antagonist).

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

1. pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
2. on-treatment period: from day of first dose of study medication to 84 days after last dose of study medication
3. post-treatment period: starting at day 84+1 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-treatment period, the **treatment-emergent** AEs. However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and/or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment overall and by treatment group (described in [Section 10.5.3.2](#) for each phase).

Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event and treatment group (described in [Section 10.5.3.1](#) for each phase).

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

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

10.5.3.3 Laboratory abnormalities

For laboratory tests covered by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, the study's biostatistical and reporting team will grade laboratory data

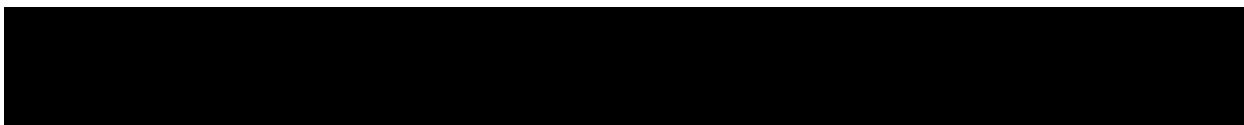


accordingly. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

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 by-treatment summaries will be generated separately for hematology, biochemistry and urinary laboratory tests:

- shift tables using CTCAE grades to compare baseline to the worst on-treatment value
- for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high)
- 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-treatment result for overall assessments
- listing of ECG evaluations for all patients with at least one abnormality.

Vital signs

Vital signs (body temperature, blood pressure, heart rate) reporting of results will include:

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

Gallbladder

Gallbladder data at each visit will be summarized and listed.

10.5.4 Patient-reported outcomes

AcroQoL total and subscale scores and EQ-5D-5L utility index and VAS scores will be generated in accordance with the respective scoring manual. The FAS will be used for analyzing patient-reported outcome data.

Descriptive statistics will be used to summarize the raw and absolute change from baseline in AcroQoL and EQ-5D-5L scores at each scheduled assessment. Patients with an evaluable baseline score and at least one evaluable post baseline score during the treatment period will be included in the change from baseline analyses.

Missing items data in a scale will be handled based on each instrument manual. All PRO analyses will include data as imputed according to the scoring manual. No imputation will be applied if the total or subscale scores are missing at a visit.



Additional analyses may be performed if deemed necessary. Such analyses will be defined in the RAP.

10.6 Interim analysis

No formal interim analysis will be performed. Primary analysis will occur after all enrolled patients complete the core phase or discontinue prior to complete this phase of the trial. Final analysis will be conducted when all patients complete the extension phase or have discontinued the study prior to completing the extension phase of the trial.

10.7 Sample size calculation

The sample size calculation was based on the primary endpoint (mean GH <1 µg/L and IGF-1 <ULN at week 36). A sample size of 100 patients was chosen to enable the estimation of proportion of patients who achieved biochemical control at week 36 with pasireotide 40-60 mg as 15%, with a precision of 7% for the associated asymptotic two-sided 95% confidence interval.

Considering a drop-out rate of 10%, the sample size required is 112.

Sample size calculation was performed using PASS 2008 software.

10.8 Power for analysis of key secondary variables

Not applicable.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

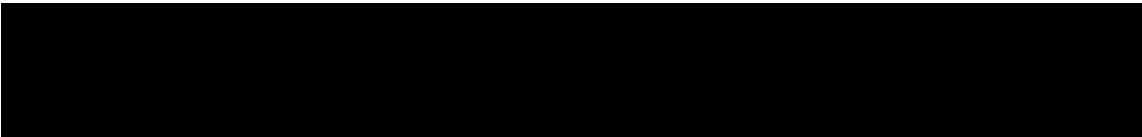
This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21) and with the ethical principles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

11.2 Responsibilities of the investigator and IRB/IEC/REB

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

11.3 Informed consent procedures

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



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

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

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

11.4 Discontinuation of the study

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

11.5.1 Communication and Publication of Clinical Trial Results

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

Novartis complies with the authorship guidelines of the International Committee of Medical Journal Editors (ICMJE) uniform requirements for manuscripts submitted to biomedical journals and other specific guidelines of the journal or congress to which the document will be submitted. These guidelines apply to any clinical trial publication including but not limited to manuscripts, abstracts, posters, and oral presentations. For more information regarding the ICMJE guidelines, visit ICMJE.org/index.html#author.

Accordingly, ALL AUTHORS MUST HAVE:

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

- Have intimate knowledge of trial implementation/analysis

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

11.6 Study documentation, record keeping and retention of documents

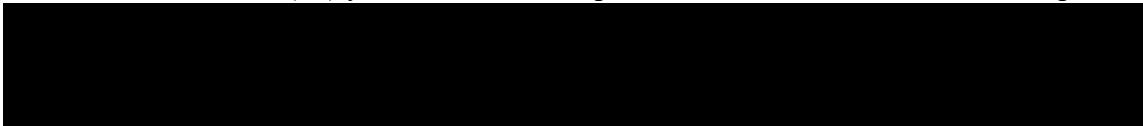
Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each 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 (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

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

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written



permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to 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.

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14 Appendices

14.1 Appendix 1: Acromegaly Quality of Life Questionnaire

ACROMEGALY- QUALITY OF LIFE QUESTIONNAIRE
(ACROQoL)

Today's date

<input type="text"/>							
Day	Month	Year					

INSTRUCTIONS FOR ANSWERING THE QUESTIONNAIRE

In the following pages there are sentences that describe some of the problems that acromegaly causes to people who, like you, suffer from this illness.

Each sentence is followed by some response options. Some of these refer to the **frequency**, while others refer to **how much you agree or disagree** with them.

Please, read each sentence carefully. Then tick the response option which best describes what you think is happening to you.

Remember that there are NO correct or incorrect answers. We are only interested in what is currently happening to you because of your acromegaly.

It is very important to answer all the questions.

Thank you very much for your collaboration

Because of my Acromegaly...**1. My legs feel weak**

- Always
 - Most of the time
 - Sometimes
 - Rarely
 - Never
- Completely agree
 - Moderately agree
 - Neither agree nor disagree
 - Moderately disagree
 - Completely disagree

4. I look awful in photographs**2. I feel ugly**

- Completely agree
 - Moderately agree
 - Neither agree nor disagree
 - Moderately disagree
 - Completely disagree
- Always
 - Most of the time
 - Sometimes
 - Rarely
 - Never

5. I avoid going out very much with friends because of my appearance**3. I get depressed**

- Always
 - Most of the time
 - Sometimes
 - Rarely
 - Never
- Always
 - Most of the time
 - Sometimes
 - Rarely
 - Never

6. I try to avoid socialising

Because of my Acromegaly...**7. I look different in the mirror**

- Completely agree
- Moderately agree
- Neither agree nor disagree
- Moderately disagree
- Completely disagree

10. People stare at me because of my appearance

- Completely agree
- Moderately agree
- Neither agree nor disagree
- Moderately disagree
- Completely disagree

8. I feel rejected by people because of my illness

- Completely agree
- Moderately agree
- Neither agree nor disagree
- Moderately disagree
- Completely disagree

11. Some parts of my body (nose, feet hands,...) are too big

- Completely agree
- Moderately agree
- Neither agree nor disagree
- Moderately disagree
- Completely disagree

9. I have problems carrying out my usual activities (e.g. working, studying, doing household tasks, family or leisure activities)

- Always
- Most of the time
- Sometimes
- Rarely
- Never

12. I have problems doing things with my hands, for example, sewing or handling tools

- Always
- Most of the time
- Sometimes
- Rarely
- Never

Because of my Acromegaly...**13. The illness affects my performance
at work or in my usual tasks**

- | | | | |
|--------------------|--------------------------|--------------------|--------------------------|
| • Always | <input type="checkbox"/> | • Always | <input type="checkbox"/> |
| • Most of the time | <input type="checkbox"/> | • Most of the time | <input type="checkbox"/> |
| • Sometimes | <input type="checkbox"/> | • Sometimes | <input type="checkbox"/> |
| • Rarely | <input type="checkbox"/> | • Rarely | <input type="checkbox"/> |
| • Never | <input type="checkbox"/> | • Never | <input type="checkbox"/> |

14. My joints ache**17. It is hard for me to
articulate words due to the size of
my tongue**

- | | | | |
|--------------------|--------------------------|--------------------|--------------------------|
| • Always | <input type="checkbox"/> | • Always | <input type="checkbox"/> |
| • Most of the time | <input type="checkbox"/> | • Most of the time | <input type="checkbox"/> |
| • Sometimes | <input type="checkbox"/> | • Sometimes | <input type="checkbox"/> |
| • Rarely | <input type="checkbox"/> | • Rarely | <input type="checkbox"/> |
| • Never | <input type="checkbox"/> | • Never | <input type="checkbox"/> |

15. I feel tired**18. I have problems with
sexual relationships**

- | | | | |
|--------------------|--------------------------|--------------------|--------------------------|
| • Always | <input type="checkbox"/> | • Always | <input type="checkbox"/> |
| • Most of the time | <input type="checkbox"/> | • Most of the time | <input type="checkbox"/> |
| • Sometimes | <input type="checkbox"/> | • Sometimes | <input type="checkbox"/> |
| • Rarely | <input type="checkbox"/> | • Rarely | <input type="checkbox"/> |
| • Never | <input type="checkbox"/> | • Never | <input type="checkbox"/> |

Because of my Acromegaly...**19. I feel like a sick person**

- Completely agree
- Moderately agree
- Neither agree nor disagree
- Moderately disagree
- Completely disagree

21. I have little sexual appetite

- Always
- Most of the time
- Sometimes
- Rarely
- Never

20. The physical changes produced by my illness govern my life

- Completely agree
- Moderately agree
- Neither agree nor disagree
- Moderately disagree
- Completely disagree

22. I feel weak

- Always
- Most of the time
- Sometimes
- Rarely
- Never

Finally, please check that you have answered all the questions.

Once again thank you very much for your collaboration.



14.2 Appendix 2: Patient Report Outcome Questionnaire EQ-5D5-L**Health Questionnaire****English version for the USA**

Under each heading, please check the ONE box that best describes your health TODAY

MOBILITY

- | | |
|----------------------------------|--------------------------|
| I have no problems walking | <input type="checkbox"/> |
| I have slight problems walking | <input type="checkbox"/> |
| I have moderate problems walking | <input type="checkbox"/> |
| I have severe problems walking | <input type="checkbox"/> |
| I am unable to walk | <input type="checkbox"/> |

SELF-CARE

- | | |
|---|--------------------------|
| I have no problems washing or dressing myself | <input type="checkbox"/> |
| I have slight problems washing or dressing myself | <input type="checkbox"/> |
| I have moderate problems washing or dressing myself | <input type="checkbox"/> |
| I have severe problems washing or dressing myself | <input type="checkbox"/> |
| I am unable to wash or dress myself | <input type="checkbox"/> |

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

- | | |
|--|--------------------------|
| I have no problems doing my usual activities | <input type="checkbox"/> |
| I have slight problems doing my usual activities | <input type="checkbox"/> |
| I have moderate problems doing my usual activities | <input type="checkbox"/> |
| I have severe problems doing my usual activities | <input type="checkbox"/> |
| I am unable to do my usual activities | <input type="checkbox"/> |

PAIN / DISCOMFORT

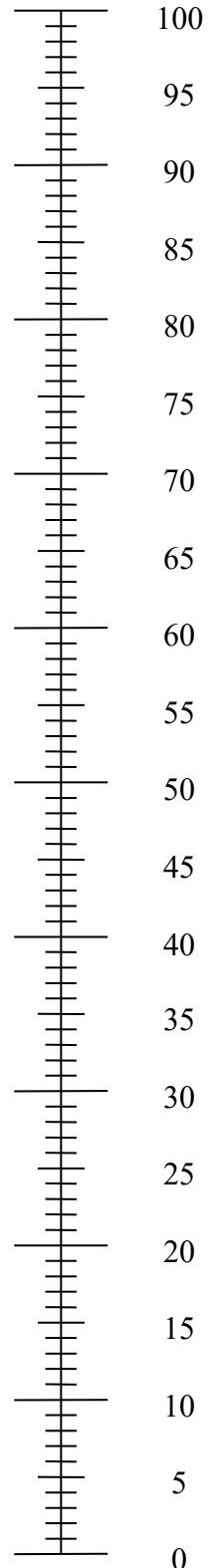
I have no pain or discomfort

I have slight pain or discomfort

I have moderate pain or discomfort

I have severe pain or discomfort

I have extreme pain or discomfort

The best health
you can imagine

ANXIETY / DEPRESSION

I am not anxious or depressed

I am slightly anxious or depressed

I am moderately anxious or depressed

I am severely anxious or depressed

I am extremely anxious or depressed

We would like to know how good or bad your health is TODAY.

This scale is numbered from 0 to 100.

100 means the **best** health you can imagine.
0 means the **worst** health you can imagine.

Mark an X on the scale to indicate how your health is TODAY.

Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

The worst health
you can imagine

14.3 Appendix 3: Concomitant Medications with “known risk of TdP (Torsades de pointes)”

The following list of drugs is generally recognized to have a possible association with TdP. This list is not considered to be all inclusive and any questions regarding concomitant medications with known risk of TdP should be discussed with the Novartis global team.

//crediblemeds.org/

14.4 Appendix 4: Pharmacy Instructions for pasireotide LAR

General Instructions

First needle for withdrawal:

All withdrawals need to be performed with a needle length of min. 50 mm, as otherwise the vial bottom is not reached, which directly affects the actual withdrawn dose. The procedures below describe the use of an 18 G needle for withdrawal, but nevertheless needles of 18 G to 20 G can be used.

Second needle for i.m. injection:

The i.m. injection should be performed with a 20 G needle, but nevertheless needles of 18 G to 20 G can be used, with a length used for standard i.m. injections.

Syringe:

The syringe recommended should have a volume of 3 ml, but 2 ml syringes (for low doses of 5 mg to 60 mg, only) or 5 ml syringes can be used as well.

Vehicle:

The vehicle for suspension is the Vehicle for microparticles, liquid in ampoules, 2 ml. (basis number 3705852).

Standing time:

For suspension in vial the standing time is 1h. As sedimentation of the suspension could lead to blocking of the needle, a standing time of 1h is allowed on constituted suspension in the vial, only. After any standing time shake the vial **up and down** at least 30 seconds in order to get a homogenous re-constituted suspension before withdrawal.

Procedure for 10 mg dosage strength (20 mg per vial)

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 an **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 (20 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 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 and by adjusting the volume in the syringe to **0.9 ml**
- Immediately, inject the whole volume of suspension intra-muscularly to the patient

Procedure for 20 mg dosage strength (20 mg per vial)

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

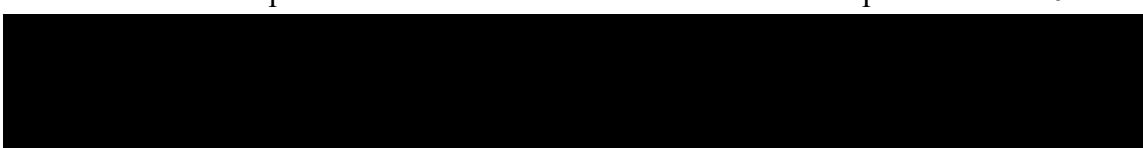
Form: MPVI

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 an **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 (20 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

Procedure for 40 mg dosage strength (40 mg per vial)

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 an **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

Procedure for 60 mg dosage strength (60 mg per vial)

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: 60 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 an **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 (60 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