Clinical Development and Medical Affairs

SOM230 Pasireotide

Clinical Trial Protocol: CSOM230D2401 / NCT01283542

An Open-Label, Single Arm, Phase II Study to Evaluate the Efficacy and Safety of Pasireotide LAR on the Treatment of Patients With Clinically Non-Functioning Pituitary Adenoma

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List of abbreviations

BID	twice a day
γ-GT	Gamma-glutamyl transpeptidase
ACTH	Adrenocorticotropic Hormone
ALP	Alkaline phosphatase
ALT	Alanine Aminotransferase/Glutamic-Pyruvic Transaminase/GPT
ANA	Antinuclear antibody
Anti-HAV	Antibody against Hepatitis A virus
Anti-HBc	Antibody against Hepatitis B core virus
Anti-HCV	Antibody against Hepatitis C virus
Anti-HEV	Antibody against Hepatitis E virus
GCP	Good Clinical Practice
BUN	blood urea nitrogen
REC	Research Ethics Committee
CMV	Cytomegalovirus
CPK	creatine phosphokinase
CRO	contract research organization
CSR	clinical study report
CTC/CTCAE	Common Toxicity Criteria/Common Terminology Criteria for Adverse Events
d	Day
LDH	Lactate dehydrogenase
SD	Standard deviation
AE	adverse event
SAE	serious adverse event
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
HBs-Ag	Hepatitis B surface antigen
EOS	End of Study
FAS	full analysis set
FSH	follicle-stimulating hormone
GH	growth hormone
HbA1c	hemoglobin subtype A_{1c} (glycated hemoglobin)
Hgb	hemoglobin
HCT	Hematocrit
HDL	high density lipoprotein
HSST	human somatostatin receptors
IB	investigator's brochure
CI	confidence interval
ICH	International Conference on Harmonization
IGF-1	insulin-like growth factor I
IgM	Immunoglobulin M

IM	intramuscular(ly)
IMS	Integrated Medical Safety
IN	investigator notification
ITT	intent-to-treat
IV	intravenous(ly)
LAR	long-acting release
LDL	low density lipoprotein
LH	luteinizing hormone
LLN	lower limit of normal
ULN	upper limit of normal
LFT	Liver Function Test
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MSAS	Memorial Symptom Assessment Scale
NFMA	clinically non-functioning pituitary macroadenoma
NFPA	clinically non-functioning pituitary adenoma
OGTT	Oral glucose tolerance test
WHO	World Health Organization
PD	Pharmacodynamics
PK	Pharmacokinetics
PRL	Prolactin
PS	Performance status
q	every
RAP	report analysis plan
RT-PCR	reverse transcriptase-polymerase chain reaction
SAP	standard automated perimetry
PFS	progression-free survival
RFS	relapse-free survival
SC	subcutaneous(ly)
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SMC	Study Management Committee
sst	somatostatin receptor subtype
SSTR	somatostatin receptor
SUSAR	suspected unexpected serious adverse reaction
PT	prothrombin time
TSH	thyroid-stimulating hormone
APTT	activated partial thromboplastin time
VEGF	vascular endothelial growth factor
WBC	White blood cells

Amendment 2

Rationale for the amendment

This amendment has been implemented to address the following items of the original protocol published for the study:

This protocol amendment includes additional liver safety measures as a result of internal medical review of pasireotide trials. During this review, 3 healthy volunteers have been identified with increased liver function tests. Three patients have met Hy's Law criteria (i.e., ALT > 3 x ULN with total bilirubin > 2 x ULN, without increase in alkaline phosphatase and any other identified cause for the abnormal findings). One patient received pasireotide 600 µg twice a day s.c. for 7 days, whereas the second patient received pasireotide 1950 µg twice a day s.c. for 5 days. The third patient (pasireotide 600 µg twice a day s.c. for 7 days) showed increased ALT and total bilirubin meeting Hy's Law criteria, but alkaline phosphatase was not evaluated and the patient received a potentially confounding concomitant medication. ALT values for all 3 patients were higher than 3 x ULN, but < 4 x ULN, and total bilirubin values were $\leq$ 4 x ULN. All 3 cases were asymptomatic, with onset 10 days after the initial administration of s.c. pasireotide, and were reversible with the discontinuation of pasireotide. None of the cases has been reported as an adverse event, and the patients completed the respective studies according to the protocol.

An assessment of the categorical abnormalities of liver enzymes was completed by the s.c. pasireotide development program (until October 2011). The 3 healthy volunteers meeting the Hy's Law criteria (including the patient without ALP value) were included among the 654 healthy volunteers, as shown below. None of the patients with Cushing's disease, carcinoid syndrome, or acromegaly in the development program met Hy's Law criteria.

- 654 healthy volunteers have been exposed to s.c. pasireotide:
  - 3 out of 654 (0.5%) met the Hy's Law biochemical criteria
  - 16 out of 654 (2.4%) patients experienced ALT or AST > 3x ULN
  - 3 out of 654 (0.5%) healthy volunteers experienced ALT or AST > 5x ULN
  - 17 out of 654 (2.6%) patients experienced total bilirubin 2x ULN (including 7 patients with preexisting liver disease and increased total bilirubin)
- 156 patients in phase 1 and phase 2 studies have been exposed to s.c. pasireotide:
  - None of the patients met the Hy's Law biochemical criteria
  - 6 out of 156 (3.8%) patients experienced ALT or AST > 3x ULN
  - 4 out of 156 (2.6%) patients experienced ALT or AST > 5x ULN
  - 2 out of 156 (1.3%) patients experienced total bilirubin $\geq$ 2x ULN
- 162 patients with Cushing's syndrome in phase 3 studies have been exposed to (s.c.) pasireotide:
  - None of the patients met the Hy's Law biochemical criteria

  - 8 out of 162 (4.9%) patients experienced ALT or AST > 3x ULN
  - 1 out of 162 (0.6%) patients experienced ALT or AST > 5x ULN
  - None of the 162 patients with Cushing's syndrome experienced total bilirubin ≥ 2x ULN
- The pasireotide Compassionate Use Program (approximately 200 patients up to October 2011) was also analyzed. One single patient with Cushing's syndrome (PHHO2010AU13717) who had been mentioned in an Investigator Notification in September 2010 was identified as meeting Hy's Law criteria.
- A review of unblinded data from the clinical program with the long-acting release (LAR) formulation of pasireotide did not show any cases meeting Hy's Law criteria.
- As a consequence from these observations, better liver safety measures must be taken to ensure patient safety.

As of the date of publication of this amendment, approximately 112 patients had been screened worldwide for the treatment. There is no expected impact from this amendment on the duration of enrollment or the publication of results.

Protocol changes

Changes in specific sections of the protocol are shown in the protocol version with tracked changes, using ~~red strikethrough font for exclusions~~ and underlined red font for insertions.

The main changes performed in the protocol, and the sections affected are detailed below:

- Protocol synopsis
  - Changes to the main body of the protocol (see items below) were also implemented in the relevant sections of the protocol synopsis.
- 5.2 Exclusion criteria
  - Exclusion criterion 8 has been replaced with a more detailed exclusion criterion still including the old information from exclusion criterion 8
  - Updated exclusion criteria 18 and 29
  - Added 2 new liver-related exclusion criteria: 30 and 31
- Table 6.2 Guidelines for the treatment of patients experiencing adverse events
  - Clarification that for liver safety monitoring, the instructions detailed in section 7.5.2.3 must be followed
- 6.6.5.1 End of treatment
  - Added new liver-related discontinuation criteria
- 7 Visits and evaluation schedule
  - Added new visit (V401) on study day 48 (week 7) for the evaluation of liver function, vital signs, adverse events, and concurrent medication

  - Separation between Chemistry and liver function tests and addition of a new line for assessments of liver function tests to describe the additional liver enzyme evaluation timepoints
  - Added new line for HBs-Ag and anti-HCV evaluations performed at screening
  - Separation of lines for APTT and PT coagulation parameters and addition of 4 PT evaluations on visits V3, V4, V401, and V5
  - Footnote E: added visit V401 to clarify that this visit is necessary only for patients treated with pasireotide LAR
  - Added footnote 14 to clarify that the new liver function and coagulation evaluations only apply to patients treated with pasireotide LAR
- 7.5 Safety
  - Added new section 7.5.2.3 Liver safety monitoring. This section describes how to treat patients who experience liver function increases especifically defined by the protocol
  - Added Figure 7-3 graphically describing liver safety monitoring procedures outlined on section 7.5.2.3
- 7.5.5.2 Coagulation
  - Added further timepoints for the evaluation of PT coagulation parameter for patients treated with pasireotide LAR
- 7.5.5.3 Chemistry
  - Definition of liver function test panel and addition of further timepoints for liver function evaluations for patients treated with pasireotide LAR
- 7.5.7 Radiology tests
  - Clarification that an abdominal ultrasound is required in case of abnormal liver function criteria
- Table 7.2 Blood collection plan for pasireotide LAR pharmacokinetics
  - Added line for unscheduled blood sample collection for pharmacokinetics in case of abnormal liver function criteria
- 10.5.4.2 Laboratory abnormalities
  - Added further liver function analysis for additional liver safety evaluations
- Annex 3.1, Table 3.1 Evaluations and visit schedule
  - Added new visit (E402) on study day 76 (week 11) for the evaluation of liver function, adverse events, and concurrent medication in the extension study
  - Separation between Chemistry and liver function tests and addition of a new line for liver function evaluations to describe additional timepoints for liver enzyme evaluations

  - Separation of APTT and PT coagulation parameter lines and addition of 5 PT evaluations on visits E2, E3, E4, E402, and E5
  - Footnote C: added visit E402 to clarify that this visit is only required for patients starting pasireotide LAR treatment in the extension study
  - Added footnote K to clarify that new liver function and coagulation evaluations apply only to patients starting treatment with pasireotide LAR in the extension study
- Annex 3, Table 3-2 Blood collection plan for pasireotide LAR pharmacokinetics
  - Added line for unscheduled blood sample collection for pharmacokinetics in case of abnormal liver function criteria
- Annex 3, 6.3 Safety analysis and parameters
  - Added further liver function analysis for additional liver safety evaluations
- Annex 3, 9.1 Special safety-related procedures
  - Added liver safety monitoring process and reference to the equivalent main study section for details of this procedure

A copy of this protocol amendment will be submitted to the Research Ethics Committee (REC) and Health Authorities. Changes to this protocol reflect the measures already implemented as part of the Expedited Safety Notification (dated November 18, 2011); however, previous approval by the REC is still required for implementation. Furthermore, the changes performed herein affect the Informed Consent Form, and the sites must update and submit for approval an Informed Consent Form taking into account the changes described in this protocol amendment.

Rationale for the Amendment

Changes to the protocol

The additions to the protocol related to the inclusion of the Extension Phase and the changes in specific sections of the protocol are described in the protocol version with tracked changes, using red strikethrough font for exclusions and red underlined font for insertions.

Rationale for the amendment

This amendment was implemented to address the following items of the original study protocol:

- Extension of the duration of treatment from week 24 to week 96:
  - In order to allow further long term safety and efficacy evaluation of the treatment with pasireotide LAR, patients who have derived benefit from treatment with this medication, according to the evaluation of the physician in charge, will be offered a 72-week extension period (i.e., patients will be followed up until week 96 and will have another safety follow-up visit on week 100)
  - A scheme including extension treatment was added (figure 4-2), in addition to the test schedule for the extension portion of the study (table 7-2). Thus, the changes implemented by this amendment are expected to be clarified
  - The duration of response evaluation for patients considered responsive until week 24 and the percentage of patients remaining with stable disease have been added to the objectives, in order to evaluate the duration of study medication efficacy
- For consistency purposes, in the pasireotide clinical trials program (SOM230), patients with uncontrolled diabetes and/or blood glucose values consistently above 275 mg/dL instead of 200 mg/dL must be withdrawn from the study, regardless of appropriate therapeutic interventions and/or whether HbA1c value is = 10 % instead of higher than 8%
- Clarification on the procedure used for QTcF prolongations.
- Correction of discrepancies and typographical errors or addition of absent secondary information seen in the original protocol:
  - In order to be consistent with the study design, the term “randomization” has been replaced with “enrollment visit (Visit 2)”, as there will be no randomization in this study, since it is single-armed
  - Changes to the protocol synopsis in order to maintain consistency with the protocol
- Clarification that only glucose and insulin will be evaluated, and not OGTT (oral glucose tolerance test)

- Clarification that the ECG and campimetry evaluations will be performed locally

Changes to the protocol

Additions to the protocol regarding the inclusion of the Extension Phase and changes in specific sections of the protocol are shown in the version with tracked changes, using red strikethrough font for exclusions and red underlined font for insertions.

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

- Protocol synopsis
  - Changes in the main body of the protocol (refer to the items below) were also implemented in the relevant sections of the protocol synopsis
  - The duration of response evaluation, the additional evaluation timepoints for patients in the extension phase, and the evaluation of the percentage of patients with stable disease have been added to the secondary objective endpoints
- 3.2 Secondary objectives
  - Weeks 48, 72 and 96 have been added as evaluation timepoints for the effect of pasireotide LAR in mean tumor volume variation, mean percent tumor volume variation, proportion of patients reaching tumor volume decrease of at least ≥ 20%, in the pituitary function, and in the alpha subunit levels
  - The following secondary objectives have been added:
    - Duration of response for extension phase patients considered as responders
    - Percentage of patients remaining with stable tumor volume during the study
- 3.2.1 Secondary objective endpoints
  - Weeks 48, 72, and 96 have been added as evaluation timepoints for mean tumor volume change, percent tumor volume change, proportion of patients reaching tumor volume decrease of at least ≥ 20%, change in the grading score for disease-related symptoms, incidence of pituitary hormone dysfunction, proportion of patients reaching alpha subunit decrease of at least 50%, and proportion of patients reaching alpha subunit normalization
  - The following secondary objective endpoints have been added:
    - Number and proportion of patients who remained responsive throughout the extension phase treatment period (according to the magnetic resonance imaging evaluations on weeks 48, 72, and 96) among patients who had been considered as responders
    - Percentage of patients remaining with stable tumor volume throughout the study (according to magnetic resonance imaging evaluations on weeks 24, 48, 72, and 96)
    - Evaluation of whether there was a difference in response between patients on pasireotide LAR 40 and 60 mg doses, if applicable

[redacted]

[redacted]

- 4 Study design
- Weeks 48, 72, and 96 have been added as evaluation timepoints for: sella turcica MRI, alpha subunit and pituitary hormone levels

[redacted]

- The study design has been changed, with the addition of an extension phase after the Main Phase (first 24 weeks) for patients who derived benefit from pasireotide LAR
  - Figure 4-2 has been added, showing the Extension Phase Study scheme
- 5 Population
  - The number of sites participating in the study has been increased, corresponding to 10 - 13 total, instead of 10 - 12
- 5.2 Exclusion criteria
  - The term “randomization” has been replaced with “enrollment visit (Visit 2)”, as there will be no randomization in this study
- 6.2 Patient numbering
  - The information that no other data will be entered in the clinical database for patients considered as screening failure has been deleted
- 6.4 Patient treatment
  - End of Study (EOS) Visit: added definition of end of extension phase, which will have a duration of up to 92 weeks or approximately 2 years, or until pasireotide or other effective therapy becomes comercially available, or until clinical benefit is no longer seen (whichever occurs first)
  - The Extension Phase has been added to the patient treatment item with the treatment description:
    - Patients will receive pasireotide LAR IM at Visit 10 and will have the first extension study visit scheduled, which will occur within 28 (± 3) days after Visit 10
    - Treatment with pasireotide LAR will be administered by the site’s healthcare professional staff every 28 (± 3) days
    - The dose will continue to be 60 mg. If a patient is receiving 40 mg due to tolerability problems and such problems have been resolved, there may be a dose escalation to 60 mg, at the physician’s discretion. If the adverse event reoccurs, the dose will be decreased to 40 mg and will be kept until completion of the Extension Phase or until study discontinuation
- Safety Follow-up
  - Extension phase added to the safety follow-up
- 6.4.2 Allowed study drug adjustments

- Added explanation for dose escalation from 40 mg to 60 mg for extension phase patients who had their doses decreased due to tolerability problems. Additionally, if the adverse event reoccurs, the dose will be decreased to 40 mg and the patient must keep this dose

- 6.4.4 Discontinuation of the study drug
  - End of Study and safety visits timepoints added to 28 ± 3 days and 56 ± 3 days after the administration of the last dose of the study medication, respectively, for extension phase patients who discontinue treatment
- 7 Visits and evaluations schedule
  - On Table 7-1
    - The information that a ± 3 day window will be allowed for scheduled visits has been deleted.
    - Clarification on item 10 that if the visual field evaluation at Screening is performed no more than 14 days after Visit 2, it may be considered baseline data and there is no need to repeat it for Visit 2
    - Item 15 deleted: At the Screening Visit and Visit 10 (EOS), blood glucose and insulin will be measured at fasting at timepoint 0 during OGTT, and will be considered as baseline data for OGTT. Regarding this change, the glucose and insulin OGTT evaluation has also been deleted from the table
  - Added Table 7-2 Visits and evaluations schedule for the Extension Study with its specifications
- 7.3 Treatments
  - Replacement of the word responsibility with accountability
  - It has been clarified that Extension Phase patients will receive the medication starting on Week 24 and every 4 weeks (28 ± 3 days) thereafter, until Week 92
- 7.4.1 Primary efficacy evaluation
  - Evaluation timepoints added on Weeks 48, 72, and 96 in the Extension Phase
- 7.4.2 Secondary efficacy evaluations
  - Visits 13, 16, 19, 22, 25, and 28 of the Extension Phase added for recording of disease-related symptoms
  - Clarification that symptoms not described in the section will be evaluated as absent or present
  - Weeks 48, 72, and 96 added for efficacy evaluation
- 7.5.2.1 Changes in blood glucose
  - 2008 ADA Position statement replaced by the 2010 statement
  - For consistency purposes, in the pasireotide clinical trials program (SOM230), blood glucose minimum levels have been changed from 200 to 275 mg/dL, as well as HbA1c percentage from 8 to 10%

- 7.5.2.2 Changes in QT interval
  - It has been clarified that if the ECG is abnormal at Visit 10 and no additional pasireotide LAR dose is administered, then the follow-up is at the investigator's discretion
  - It has been clarified that, on Scenario B of ECG change, the Holter ECG test must be recorded as soon as possible, within 7 days after the initial abnormal ECG, and not 30 minutes before dosing on the next pasireotide LAR administration day
  - Figure 7-1
    - Week 6 has been replaced with week 7 for QTcF evaluation
    - Deleted recommendation for PK sample collection
  - Figure 7-2
    - Week 7 has been replaced with week 6 for QTcF evaluation
    - Deleted recommendation of Holter ECG on visit 4 or visit 8
    - Deleted recommendation for PK sample collection
- 7.5.3 Physical examination, weight, height
  - CRF has been corrected to eCRF
- 7.5.4 Vital signs
  - Visits 13, 16, 19, 22, 25, 28, and 29 have been added for the evaluation of vital signs in the extension phase
- 7.5.5 Performance Status
  - Visits 13, 16, 19, 22, 25, 28, and 29 have been added for the evaluation of Performance Status in the extension phase
- 7.5.6.1 Hematology and Coagulation
  - It has been clarified that the hematology parameters will be evaluated in the Screening Period and before administration of the study drug, and assessment on Visit 2 has been deleted
  - It has been clarified that in the Extension Phase the evaluations will be performed first on Visit 10, and every 6 months thereafter
- 7.5.6.2 Chemistry
  - Deleted Chemistry evaluation on Visit 2
  - Chloride and inorganic phosphorus tests have been added to the chemistry evaluation
  - Deleted OGTT evaluation
  - It has been clarified that fasting blood glucose, insulin, fasting chemistry evaluations, and HbA1c will also be performed on Weeks 48, 72, and 96 in the Extension Phase, and that the vitamin B12 and folic acid evaluations will also be performed on weeks 48 and 96 in the Extension Phase

[redacted]

- 7.5.6.4 Urinalysis

  - It has been clarified that urine evaluations will also be performed on weeks 48, 72, and 96 in the Extension Phase
- 7.5.6.5 Pregnancy test
  - It has been clarified that the pregnancy test will be performed on weeks 48, 72, and 96 in the Extension Phase
- 7.5.7 Radiology tests
  - It has been clarified that the gallbladder ultrasound will be performed on weeks 48 and 96 in the Extension Phase
  - It has been clarified that the MRI scans will be performed on Weeks 48, 72, and 96 in the Extension Phase
- 7.5.8 Electrocardiogram (ECG)
  - It has been clarified that, in the Extension Phase, the ECG will be performed on weeks 36, 48, 60, 72, 84, and 96
  - The information that three copies of the ECGs will be made and one will be submitted for evaluation by an ECG central evaluator has been deleted
- 7.5.9 Visual evaluations
  - Deleted recommendation that the visual field test must be performed and processed according to the guidelines of the central evaluator's facility, which will be distributed to the sites before study start
- 9.3 Database management and quality control
  - It has been clarified that the results from the laboratory samples that will be centrally processed will be submitted to the investigator and not to Novartis (or the designated CRO)
  - The information that the captured biomarker sampling information will be handled by a CRO designated by Novartis and that it will be electronically collected and transfered by a Novartis internal sample tracking system has been deleted
- 10 Statistical methods and data analysis
  - It has been clarified that a final analysis will be performed when all Extension patients complete their last visit and will be reported either as an additional clinical study report or as a Main Phase report amendment
  - It has been clarified that statistical methods similar to those of the main phase will be used in the analysis throughout the extension phase, as appropriate

[redacted]

- 11.5.1 History of amendments
  - Clarifies the reason for amendment

REC Approval

A copy of this amended protocol will be submitted to the Research Ethics Committee (REC) and to the Health Authorities.

The changes described in this amendment require REC approval previous to implementation. Additionally, if the changes made herein affect the Informed Consent Form, the sites must update a reviewed Informed Consent Form and submit it for approval, considering the changes described in this protocol amendment.

Synopsis of the oncology clinical trial protocol

Investigational drug	Pasireotide LAR (SOM 230)
Protocol number	**CSOM230D2401**
Study phase	II
Study title	An Open-Label, Single Arm, Phase II Study to Evaluate the Efficacy and Safety of Pasireotide LAR on the Treatment of Patients with Clinically Non-Functioning Pituitary Adenoma
Background	Pre-clinical: Pasireotide (SOM230) is a new cyclohexapeptide containing the structural elements [(2-aminoethyl) amino carbonyl oxy]-L-proline, phenylglycine, and tyrosine (benzyl). It is a somatostatin analogue with a wide binding profile to its receptors, which may result in better efficacy in the current indications of octreotide (e.g., acromegaly and gastro-entero-pancreatic neuroendocrine tumors) and potential efficacy in new indications. Like natural somatostatin and other somatostatin analogues, pasireotide performs its pharmacological activity by binding to somatostatin (sst) receptors. Pasireotide shows a unique high-affinity binding profile to four of the five known human somatostatin receptors (sst1, 2, 3 and 5). Compared to octreotide, pasireotide has a binding affinity 30 to 40 times higher for sst1 and sst5 receptors, 5 times higher for sst3 receptors, and a comparable affinity for sst2 receptors. Pasireotide has two formulations in complete clinical development, namely, the SC (subcutaneous) and the IM (intramuscular) LAR (long-acting release) formulations. Pharmacokinetics: In healthy volunteers [CSOM230C2101], single IM injections of 40 mg and 60 mg of pasireotide LAR showed typical long-acting release concentrations, which were characterized by an initial peak on day 1, followed by a long-acting release. Pasireotide LAR has been tested in patients with acromegaly and patients with carcinoid tumors who received IM injections once a month for three months at 20, 40 and 60 mg doses in a Phase I study [CSOM230C2110]. The PK analysis has shown that steady-state was reached with three monthly injections of pasireotide LAR. Pasireotide residual plasma concentrations (pre-dose) on days 28, 56, and 84 indicated that the pharmacokinetic exposures were approximately dose-proportional. The pharmacokinetic exposure proportion among study populations was healthy volunteers : patients with acromegaly : patients with carcinoid tumors = ~ 1 : 1 : 2 for pasireotide LAR, similarly to the proportion for subcutaneous pasireotide. Clinical Trials: The pasireotide LAR formulation has been investigated in three studies: [CSOM230C2101] in healthy volunteers, [CSOM230C2110] in patients with acromegaly and carcinoid tumors, and [CSOM230C2305] – the registration program currently ongoing in patients with acromegaly. The [CSOM230C2101] study evaluating single intramuscular (IM) doses of pasireotide LAR 40 and 60 mg (N = 5 by dose cohort) in healthy volunteers has shown that pasireotide LAR was well tolerated and that there was no difference in the frequency of AEs observed between pasireotide LAR and octreotide LAR. The most common AE was diarrhea, sometimes associated to abdominal pain and/or flatulence. Gastrointestinal events were mild or moderate in intensity. Approximately half of the subjects reported mild transient pain at the injection site. Two volunteers on the 60 mg dose showed mildly increased fasting blood

	glucose (< 123 mg/dL) levels, with all values returning to normal 28 days after the LAR injection. The [CSOM230C2110] study has evaluated single IM doses of pasireotide LAR of up to 60 mg in patients with acromegaly or carcinoid disease. Preliminary results of the clinical efficacy, safety, and pharmacokinetics / pharmacodynamics (PK/PD) analysis are available for 35 patients with acromegaly, including 10, 12, and 13 patients in pasireotide LAR dose groups of 20, 40, and 60 mg. This study has also shown that pasireotide LAR was generally well tolerated, and that the most common AEs seen were gastrointestinal and mild in intensity. The [CSOM230C2305] study is evaluating the efficacy and safety of pasireotide LAR in patients with acromegaly (without medical care) compared to octreotide LAR. This study is still ongoing.
Purpose / rationale	Pasireotide LAR (SOM230) is a new somatostatin analogue with properties similar to those of natural somatostatin and, specifically, high-affinity and functional activity to sst 1, sst 2, sst 3, and sst 5. Pasireotide has been shown to inhibit GH and prolactin secretion of in vitro pituitary adenomas, in vitro and in vivo ACTH, and in vivo GH/IGF-1. Additionally, pasireotide has inhibited the proliferation of endothelial VEGF-stimulated cells. A pre-clinical trial showed that pasireotide avoids NFPA cell viability by inhibiting VEGF secretion, indicating that this multi-receptor SSTR agonist may be useful as a medical therapy for NFPA. Pasireotide LAR has been tested in clinical trials in healthy volunteers [CSOM230C2101] and in 2 patient populations (i.e., acromegaly and carcinoid disease [CSOM230C2101]). However, there are no previous reports regarding the clinical use of pasireotide LAR in NFPAs. Based on these findings and on the need for a medical therapy that may be used pre-surgically to improve surgical results, leading to less patients with remaining tumors, or to control tumor growth or recurrence after surgery, avoiding the need for radiation therapy, pasireotide LAR may be a good option for treatment, both as pre-surgery therapy and in post-surgery tumor growth control.
Objectives	Primary: • To evaluate the efficacy of pasireotide LAR in the proportion of patients with NFPA reaching treatment response. **Secondary:** • To evaluate the effect of pasireotide LAR in mean tumor volume variation between baseline and treatment weeks 4, 12, 24, 48, 72, and 96. • To evaluate the effect of pasireotide LAR in mean percent tumor volume variation between baseline and treatment weeks 4, 12, 24, 48, 72, and 96. • To evaluate the effect of pasireotide LAR in the proportion of patients reaching tumor volume decrease of at least ≥ 20% after treatment weeks 4, 12, 48, 72, and 96. • To evaluate the effect of pasireotide LAR on time to tumor response. • To evaluate the effect of pasireotide LAR on disease-related symptoms* *Disease-related symptoms to be evaluated: headache, visual disorders, fatigue, decreased libido, erectile dysfunction (only for men), and menstrual irregularity or interruption (only for non-menopausal women). • To evaluate the effect of pasireotide LAR on the pituitary function on

	weeks 4, 12, 24, 48, 72, and 96. • To evaluate the effect of pasireotide LAR on the alpha subunit levels on weeks 4, 12, 24, 48, 72, and 96. • To evaluate the overall safety and tolerability of pasireotide LAR. • For extension phase: duration of response for patients considered as responders (i.e., patients reaching a tumor volume decrease of at least 20% compared to the initial tumor volume). • To evaluate the percentage of patients remaining with stable tumor volume throughout the study. [redacted]
Endpoints (efficacy, safety)	Primary Objective Endpoint: • Proportion of patients with NFPA reaching tumor volume decrease of at least 20% after the 24-week treatment with pasireotide LAR. **Secondary Objectives Outcomes:** • Mean tumor volume change evaluated by pituitary MRI between baseline and weeks 4, 12, 24, 48, 72, and 96. • Percent tumor volume change evaluated by pituitary MRI between baseline and weeks 4, 12, 24, 48, 72, and 96. • Proportion of patients reaching tumor volume decrease of at least ≥ 20% after 4, 12, 48, 72, and 96 treatment weeks. • Time to treatment response for treatment responders, defined as the time from the first injection to the first evaluation in which the patient reached a tumor volume decrease of at least ≥ 20%. • Change in the grading score for disease-related symptoms between baseline and weeks 4, 12, 24, 48, 72, and 96. • Incidence of pituitary hormone dysfunction on baseline and weeks 4, 12, 24, 48, 72, and 96. • Proportion of patients reaching alpha subunit decrease of at least 50% on weeks 4, 12, 24, 48, 72, and 96. • Proportion of patients reaching alpha subunit normalization on weeks 4, 12, 24, 48, 72, and 96. • Percentage of adverse events with CTC grade ≥ 3 during treatment with pasireotide LAR. • Percentage of patients with at least one adverse event with CTC grade ≥ 3. • Incidence of all adverse events, incidence of abnormal laboratory values, and summary of laboratory evaluations. • For the extension phase: among patients considered as responders (i.e., patients reaching a tumor volume decrease of at least 20% compared to the initial tumor volume), evaluate the number and proportion of patients remaining responsive throughout the extension phase treatment period (according to magnetic resonance imaging evaluations on weeks 48, 72, and 96). • To evaluate the percentage of patients remaining with stable tumor volume throughout the study, i.e., patients mantaining a tumor volume variation of less than 20% in relation to baseline tumor volume (according to magnetic resonance imaging evaluations on weeks 24, 48, 72, and 96).

	[redacted]
Study design	A Phase II, open-label, single-arm, prospective, multicenter study to evaluate the efficacy and safety of pasireotide LAR 60 mg in adult patients with NFPA. Main Phase: During the main phase of the study, visits will be performed every 28 ± 3 days, with 2 extra safety visits on days 20 and 76. For all evaluations and visits of the Main Phase, see Table 7-1. Eligible patients will receive pasireotide LAR 60 mg every 28 ± 3 days for 24 weeks, during the Main Phase of the study. Dose decreases to 40 mg will be allowed, due to safety issues. In case of rapid deterioration of the visual field or sudden visual loss, the patient will be discontinued from the study. Extension Phase: After the main phase of the study (first 24 weeks of treatment), patients who have derived benefit from treatment with pasireotide LAR, according to the evaluation by the physician in charge, will be offered the opportunity to enter the Extension Phase. Patients will continue to receive pasireotide LAR in 4-week intervals for up to 92 weeks or until pasireotide or other effective therapy becomes commercially available or until clinical benefit is no longer noticed (whichever occurs first). For all evaluations and visits in the Extension Phase, see Table 7-2.
Population	The population for this study is composed of adults diagnosed with NFPA who did not receive previous therapy (treatment-naïve) for the disease. Due to the difficulty to evaluate changes in tumor volume in microadenomas, and also because they may be mistakenly diagnosed as incidentalomas, only patients with macroadenomas (≥ 1 cm) may be enrolled in the study.
Inclusion / exclusion criteria	Inclusion: • Male and female patients ≥ 18 years old • Patients with clinically non-functioning pituitary macroadenomas ≥ 1 cm • No previous treatment for NFPA • Eastern Cooperative Oncology Group (ECOG) Performance status (PS) of 0 to 1 • Written Informed Consent Form obtained before any screening procedure Exclusion: • Patients requiring surgical intervention for relief of any sign or symptom related to tumor compression

	• Previous pituitary surgery • Previous medical treatment for pituitary tumor • Patients who received pituitary radiation within 10 years previous to the enrollment visit (visit 2) • Prolactin (PRL) levels > 100 ng/mL (PRL evaluation must be performed with diluted samples in order to ensure prevention of the "hook effect") • Patients with optic chiasm compression, causing clinically significant acute defects on visual field • Diabetic patients whose blood glucose is poorly controlled, as confirmed by HbA1C > 8% • Patients with known gallblader or bile duct disease, acute or chronic pancreatitis (patients with asymptomatic cholelithiasis and asymptomatic dilation of the bile duct may be enrolled) • Patients with abnormal coagulation (increased PT or APTT 30% above normal limits) or patients who received anticoagulants affecting PT (prothrombin time) or APTT (active partial thromboplastin time) • Patients experiencing congestive heart failure (NYHA Class III or IV), unstable angina, persistent ventricular tachycardia, ventricular fibrillation, advanced heart blockade, or history of acute myocardial infarction within 24 weeks previous to the enrollment visit (visit 2) • Screening (Visit 1) or baseline (pre-dose, visit 2) QTcF > 450 msec • Patients with history of syncope or family history of sudden idiopathic death • Patients with persistent or clinically significant cardiac arrhythmias • Patients with Torsades de Pointes risk factors, such as uncorrected hypopotassemia, uncorrected hypomagnesemia, heart failure, clinically significant / symptomatic bradycardia, or high degree AV block • Patients with concurrent disease(s) that may prolong QT interval, such as autonomous neuropathy (caused by diabetes or Parkinson's disease), HIV, cirrhosis, uncontrolled hypothyroidism, or heart failure • Patients taking medication(s) known to prolong QT interval • Patients with liver disease or history of liver disease, such as cirrhosis, chronic active hepatitis B and C or persistent chronic hepatitis, or patients with ALT and/or AST > 2 x ULN, total blood bilirubin >1.5 x ULN, and blood albumin < 0.67 x LLN • Patients with WBC count < 3x 10^9/L; Hgb < 90% LLN; platelets < 100x 10^9/L • Patients with any current or previous medical condition that, in the investigator's opinion, may interfere with the conduction of the study or the evaluation of the study results • Patients with history of immunological impairment, including a positive result for HIV tests (ELISA and Western blot). An HIV test will not be required; however, previous medical history will be analyzed • Patients with known hypersensitivity to somatostatin analogues or any other pasireotide LAR component • Patients with active malignant disease within the last five years (except for basal cell carcinoma or in situ cervix carcinoma) • Patients with presence of uncontrolled, acute suspected, or active chronic infection

	• Pregnant or breastfeeding patients, or patients of childbearing potential, who do not adopt a clinically acceptable contraceptive method. If a woman is participating in the study, then a contraceptive method will be sufficient (pill or diaphragm), and the male partner must use condoms. If an oral contraceptive is used in addition to condoms, the patient must have adopted this method for at least 2 months prior to enrollment in the study, and must agree to continue to use the oral contraceptive throughout the study, and for three months after the end of the study. Sexually active male patients are required to use condoms throughout the study and for three months after the end of the study, as a precautionary measure (available data do not suggest any increase in reproductive risk with the study drugs) • Study participants on an investigational drug 30 days before the enrollment visit (visit 2). Patients must have recovered from all side effects from other investigational therapies. • Patients with history of non-compliance to medical treatments, patients considered non-compliant, or any circumstance at the time of enrollment in the study that might prevent the completion of the entire study or required follow-up • Patients experiencing improper use/abuse of alcohol or drugs, in the past or currently, within 12 months before visit 1 (screening) • Presence of Hepatitis B surface antigen (HBs-Ag) • Presence of antibody screen for Hepatitis C (anti-HCV) • Patients undergoing major surgery / surgical therapy for any cause within 4 weeks before randomization • Patients with confirmed hypothyroidism, hypoadrenalism, and hypogonadism (except physiological andropause and menopause), unless properly treated with stable doses of hormone replacement therapy for at least 3 months before study entry • Patients on growth hormone replacement therapy • Patients with uncontrolled cardiovascular, renal, or metabolic disorders • Patients with severe neurological or psychiatric disorders • Patients with contraindication to MRI, such as, for example (but not limited to): brain aneurysm clips, cardiac pacemaker, internal wiring of cardiac pacemaker and temporary pacemaker, cochlear implants, hearing devices containing internal and non-removable parts, Swan-Ganz catheter, aortic balloon, Zenith AAA Endovascular Graft, and other possible contraindications related to ferromagnetic materials identified in the patient's interview.
Patient numbering	Each study patient is uniquely identified by a 6-digit patient number, which is a combination of the 3-digit site number and the 3-digit subject number.
Investigational and control drugs	Depot IM pasireotide LAR (long-acting release) injection. (Pasireotide LAR excipients include: mannitol, sodium carmellose (sodium carboxymethyl cellulose), poloxamer 188, and water for injection).
Control drug	Not applicable
Dose, schedule, treatment cycle	<u>Main Phase:</u> The study drug is pasireotide LAR at a 60 mg dose every 28 ± 3 days, for 6 months, administered as intragluteal depot IM injection by the clinical staff or healthcare professional at each research site. The first 60 mg dose of IM pasireotide LAR will be administered on Visit 2, after all baseline evaluations are completed and the eligibility to participate in the study is confirmed. For patients unable to tolerate the dosage schedule specified in

<table>
<tr><td></td><td>the protocol, a dose decrease to 40 mg is allowed. Patients unable to tolerate the minimum pasireotide LAR dose of 40 mg will be discontinued from the study.

<u>Extension Phase:</u>
After the Main Phase of the study (first 24 weeks of treatment), patients benefiting from treatment with pasireotide LAR will be offered the opportunity to continue to receive pasireotide LAR, based on the physician’s evaluation and the patient’s wishes. Patients participating in the Extension Phase will be treated with pasireotide LAR for up to 92 weeks, or until pasireotide or other effective therapy becomes commercially available, or until clinical benefit is no longer seen (whichever occurs first).

Patients enrolled in the Extension Phase will receive pasireotide LAR at the same dose used during the Main Phase. The first dose will be administered on Visit 10 (End of Main Phase [EOS] Visit, which will correspond to the Extension Phase baseline visit) and will have the next Extension Phase visit scheduled, which will occur after 28 (± 3) days. Pasireotide LAR will be administered by the site’s healthcare professional staff every 28 (± 3) days during the Extension Phase.
Patients who will not participate in the Extension Phase must perform Visit 11 (Follow-up Visit) of the Main Phase.</td></tr>
<tr><td>Supply, preparation, and administration</td><td>Novartis will provide pasireotide LAR, as 20 and 40 mg of powder in vials and 2 mL of vehicle in ampoules (for reconstitution), provided in cartons.
Pasireotide LAR must be prepared as follows:
<table>
<tr><td>Dose (mg)</td><td>Volume to be injected</td></tr>
<tr><td>60 mg</td><td>1 20 mg vial + 1 40 mg vial + 2 mL of vehicle;
total volume to be injected</td></tr>
<tr><td>40 mg</td><td>1 40 mg vial + 2 mL of vehicle: total volume
to be injected</td></tr>
</table></td></tr>
<tr><td>Visits and evaluations schedule</td><td><u>Screening Visit:</u>
Performed from Day -28 to Day -1 (Visit 1). Patients will receive the Informed Consent Form and, after signing it, they will be subjected to evaluations, including demographics, diagnosis and extent of disease, relevant / current medical history, verification of inclusion / exclusion criteria, vital signs, physical examination, ECOG performance status, ECG, blood pregnancy test, hematology and coagulation test, urinalysis, glucose and fasting blood insulin, HbA1c, chemistry, vitamin B12 and folic acid, hormone evaluation, alpha subunit evaluation, [redacted], visual field evaluation, gallblader ultrasound, pituitary / sella turcica MRI, and evaluation of concurrent medication and disease-related symptoms.

<u>Main Phase:</u>
Inclusion will occur on Day 0 (Visit 2). Visits will occur as scheduled: Visit 3 (Day 20, Week 3), Visit 4 (Day 28, Week 4), Visit 5 (Day 56, Week 8), Visit 6 (Day 76, Week 11), Visit 7 (Day 84, Week 12), Visit 8 (Day 112, Week 16), Visit 9 (Day 140, Week 20), Visit 10 or End of Main Phase Visit (Day 168, Week 24) and, if the patients do not enter the Extension Phase, Follow-up Visit on Week 28, Day 196. A ± 3-day deviation from the scheduled visit will be allowed.</td></tr>
</table>

	Patients will receive the study medication on Visits 2, 4, 5, 7, 8, 9, and 10 (if they enter the Extension Phase). Patients will perform hematology, urinalysis, fasting blood glucose, and chemistry tests, as well as a visual field evaluation and a gallblader ultrasound, as per table 7-1. ECG, ECOG performance status, and evaluation of symptoms and of potential AEs will be performed on all visits. A pituitary MRI with gadolinium will be performed on Visits 1, 4, 7, and 10. Hormone and alpha subunit evaluations will be performed on Visits 1, 4, 7, and 10. [redacted] For all visits and evaluations, see Table 7-1. Extension Phase: Enrollment will occur on Day 168 ± 3 (Week 24, Visit 10). Patients enrolled in the Extension Phase will receive pasireotide LAR IM on Visit 10, or End of Main Phase (EOS) Visit, and will have the next Extension Phase visit scheduled, which will occur 28 (± 3) days after Visit 10. Treatment with pasireotide LAR will be administered every 28 (± 3) days (see Table 7-2). MRI and visual field evaluations will be performed every 24 weeks (Weeks 24, 48, 72, and 96). ECG and symptom evaluations will occur every 12 weeks (± 3 days) and other safety (hematology, coagulation, and chemistry) and efficacy evaluations will occur every 24 weeks (± 3 days). For all Extension Phase evaluations, refer to Table 7-2. If a patient reports sudden worsening of visual field, extra visual field examinations and MRIs will be allowed.
Efficacy evaluation(s)	Tumor volume, hormone response, and relevant disease-related symptoms will be evaluated. Primary evaluation: The primary efficacy parameter – tumor volume decrease ≥ 20% – will be evaluated by MRI with gadolinium contrast in the Screening Phase (this will be considered as baseline imaging) and on Weeks 4, 12, and 24. Response is defined as a ≥ 20% decrease in tumor volume. The primary endpoint is the proportion of patients reaching a tumor volume decrease ≥ 20% after 24 weeks of treatment with pasireotide LAR. Secondary evaluations: Based on the tumor volume evaluations described above, variations in mean tumor volume and mean percent tumor volume change will be evaluated on Weeks 4, 12, and 24, as well as the time to response (i.e., time from the first dose of pasireotide LAR to the moment when the patient reaches a tumor volume decrease ≥ 20%). Tumor volume evaluations in the Extension Phase will occur on Weeks 48, 72, and 96, in addition to week 24, as described above. Other secondary efficacy parameters include disease-related symptoms reported by patients and recorded by the investigator or his/her designees.

	The following disease-related symptoms will be evaluated: headache, visual disorders, fatigue, decreased libido. Only for men: erectile dysfunction. Only for non-menopausal women: irregular or interrupted menstrual cycles. The investigator will also ask patients to classify the symptoms above according to a 5-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe). Hormone profiles, including growth hormone (GH), insulin-like growth factor I (IGF-1), follicle-stimulating hormone (FSH), luteinizing hormone (LH), adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), prolactin (PRL), cortisol, free T4, and estradiol (only for women) or testosterone (only for men), will be evaluated in the screening period (and will be considered as baseline data) and on Weeks 4, 12, and 24 of the Main Phase. Extension Phase evaluations will be performed on Weeks 48, 72, and 96, in addition to week 24, as described above. Subunit-alpha levels will be measured in the Screening Period (and will be considered as baseline data), on Weeks 4, 12, and 24 in the Main Phase, and on Weeks 48, 72, and 96 in the Extension Phase, in addition to week 24, as described above. [redacted]
Special safety evaluation(s)	<u>Changes in blood glucose:</u> Patients with history or recent diagnosis of fasting glucose impairment, glucose tolerability impairment, diabetes mellitus, or at risk of developing these conditions must monitor blood glucose via the fingerstick capillary glucose test twice a day (fasting and 2-hour postprandial). It is recommended that patients be encouraged to keep a blood glucose diary for appropriate control of the disease throughout the study, as well as present the data collected to the physician / diabetes expert for evaluation. The data will not be collected by the sponsor. It is advised that any patient presenting fasting plasma glucose > 130 mg/dL (7.2 mmol/L), or 2-hour postprandial capillary glucose (PPG) ≥ 180 mg/dL (10 mmol/L) in two consecutive measurements with an interval of approximately 14 days and/or HbA1c > 7% be evaluated by a diabetes expert for appropriate treatment. <u>Changes in QT interval:</u> If, at any visit, a QTcF > 480 msec is seen in patients receiving pasireotide LAR, the following actions will be taken: • A visit to the cardiologist must be scheduled as soon as possible, but in no more than 7 days from the initial abnormal ECG, and the cardiologist must reevaluate the ECG (this may be done by the central cardiologist, if the study has one).

	• If a QTcF > 480 msec is NOT confirmed, no action will be taken. • If a QTcF > 480 msec is confirmed, a cardiologist must perform a thorough examination (such as review of the baseline ECG, concurrent medication, and performance of cardiovascular examination (including at least one cardiac auscultation)) in order to evaluate the patient for cardiovascular risk factors. • If, based on the cardiologist's evaluation, the investigator considers that there is an acute cardiovascular safety risk, and that the patient should not continue to receive the study drug, or the patient meets any discontinuation criteria (section 6.4.5.1), he/she must be immediately discontinued. • If, after the cardiologist's analysis, the investigator considers that there is no acute cardiovascular safety risk and that the patient may continue to receive the study drug, a Holter ECG (24 hours) must be performed, depending on when the initial ECG was performed.
Patient-reported outcomes	Not applicable.
Pharmacokinetics	Not applicable.
Biomarker evaluations	Not applicable.
Statistical methods and data analyses	<u>Populations for Analysis:</u> Full analysis set (FAS): comprises all patients successfully completing Screening and receiving at least one dose of the study medication. The FAS will be the primary set for efficacy analyses. Safety analysis set: comprises all patients receiving at least one dose of the study drug and who had at least one post-baseline safety evaluation. The analyses described in this section represent the analyses to be used in the Main Phase of the study. A final analysis will be performed when all Extension patients complete their last visit and will be reported either as an additional clinical study report or as an amendment to the Main Phase report. <u>Primary Objective:</u> The primary efficacy variable is the proportion of patients with NFPA reaching tumor response, defined as tumor volume decrease of at least 20% after 24 weeks of treatment with pasireotide LAR. The response rate will be summarized in terms of incidence rates and the 90% confidence interval at the end of the Main period of the study (Week 24). The same analysis will be repeated for the PPS population. <u>Secondary Objectives:</u> All secondary efficacy analyses will be based in the full analysis set (FAS). The safety analysis set will be used for all safety analyses. The secondary efficacy endpoints are described in section 3.3.2. <u>Safety:</u> The safety evaluation will be based mainly on the frequency of adverse events (AEs) and on the number of patients with laboratory values outside the reference ranges. Other safety data, such as physical examination, weight, height, vital signs, ECOG performance status, radiology tests, ECGs, MRIs, and visual evaluations, will be summarized as appropriate.

<table>
<tr><td></td><td>Calculation of the Sample Size:
The sample size of 19 patients has been selected regardless of statistical power. A response rate (tumor volume decrease ≥ 20%) of at least 10% of patients is considered clinically significant for this population. If the actual response rate is 10%, the probability of obtaining two or more responders among the 16 patients is 58%. In this study, the exact 90% CI will also be obtained. The table below shows the exact 90% CI when 2 - 6 patients, among the 19 patients, respond. Considering a drop-out rate of 20%, 23 patients will be enrolled in order to obtain 19 evaluable patients for the final analysis.
<table>
<tr><th>Responders / n</th><th>Lower confidence limit</th><th>Upper confidence lir</th></tr>
<tr><td>2/19</td><td>1.9%</td><td>29.6%</td></tr>
<tr><td>3/19</td><td>4.4%</td><td>35.9%</td></tr>
<tr><td>4/19</td><td>7.5%</td><td>41.9%</td></tr>
<tr><td>5/19</td><td>11%</td><td>47.6%</td></tr>
<tr><td>6/19</td><td>14.7%</td><td>53%</td></tr>
</table></td></tr>
<tr><td>Planned Dates</td><td>FPFV: August 2011</td><td>LPFV: April 2012</td></tr>
<tr><td>Number of patients, sites, and location of the sites</td><td colspan="2">Total number of patients: 23
Number of sites: 13
Location of the sites: Brazil</td></tr>
</table>

1 Background

1.1 Summary of clinically non-functioning pituitary adenomas (NFPAs)

Approximately 10% of intracranial neoplasms are pituitary gland tumors, the most common being pituitary adenoma, with an annual incidence of 0.5 to 8.2 subjects per 100,000 (Asa 2008)(Ezzat et al 2004)(Jane et al 2003). Tumors from this heterogeneous group have been commonly classified by their sizes: lesions < 1 cm are considered microadenomas and those ≥ 1 cm are macroadenomas (Ezzat et al 2004)(Jaffe 2006).

Pituitary adenomas are frequently not diagnosed and may be asymptomatic. Up to 1 in every 600 people may present non-diagnosed macroadenomas (Ezzat et al 2004). A recent meta-analysis has reported an estimated prevalence rate of 16.7% for asymptomatic individuals, 14.4% for postmortem, and 22.5% for radiological studies (Ezzat et al 2004).

The types of pituitary adenomas are presented on Table 1-1. Specific hormones are secreted by corticotropic, somatotropic, thyrotropic, gonadotropic, and lactotropic adenomas. NFPAs do not cause any specific clinical syndrome, but patients may experience symptoms related to hypopituitarism and mass effect, such as headache, visual impairment, and fatigue. NFPAs are responsible for approximately 25% to 35% of surgically resected tumors (Jane et al 2003).

Table 1-1 Pituitary adenomas, main associated hypersecreted hormone, and related clinical syndrome

Pituitary ademona	Main associated hypersecreted hormone	Clinical syndrome related to hormone hypersecretion
Corticotropic adenoma	Adrenocorticotropic hormone (ACTH)	Cushing's disease
Somatotropic adenoma	Growth hormone (GH)	Acromegaly / Gigantism
Thyrotropic adenoma	Thyroid-stimulating hormone (TSH)	Hyperthyroidism (may be asymptomatic)
Gonadotropic adenoma	Luteinizing hormone (LH) Follicle-stimulating hormone (FSH) and subunits	Usually asymptomatic
Lactotropic adenoma	Prolactin (PRL)	Galactorrhea, hypogonadism, amenorrhea, infertility, impotence
Clinically non-functioning pituitary adenoma (NFPA)	Clinically insignificant hormone secretion (alpha subunit may be increased)	Usually asymptomatic

All pituitary macroadenomas may cause symptoms related to the tumor mass (tumor compression symptoms), such as headache, visual field impairment, and hypopituitarism-related symptoms.

Hypopituitarism may occur in pituitary macroadenomas as a result of (a) compression of the pituitary stalk, leading to a decrease of hypothalamic hormones reaching the pituitary gland; (b) compression of the normal pituitary tissue; and (3) hypothalamic involvement of the pituitary tumor (Dekkers et al 2008). The hypogonadism seen with these adenomas is frequently associated to the increase in blood prolactin levels (usually < 200 ng/mL) (Jaffe 2006). Patients with hypopituitarism are at increased risk of mortality due to cardiovascular, cerebrovascular, and/or respiratory disease (Bates et al. 1996)(Rosen et al. 1990)(Bulow et al 1997)(Nilsson et al 2000)(Tomlinson et al 2001).

Hypopituitarism due to NFPA may produce different symptoms. Four out of five patients with NFPA experience secondary hypothyroidism, and 3 out of 5 experience secondary adrenal failure (Jaffe 2006). Most patients also experience signs and symptoms of hypogonadism, frequently as a result of direct compression by a large adenoma and growth hormone (GH) deficiency (Jaffe 2006). Approximately 60% to 80% of patients experience visual field defects, a consequence of tumor pressure on the optic chiasm (Jaffe 2006)(Dekkers et al 2007). In some cases, these tumors compress other surrounding brain tissues and lead to dysfunctions in the cranial nerves (Jaffe 2006)(Vance 2008). Frequently, patients experience headache, although this event is not diagnosed (Vance 2008).

The evaluation of the tumor volume and location of the pituitary adenoma are performed more efficiently by magnetic resonance imaging (MRI) (Dekkers et al 2008). Screening hormone tests that may determine pituitary deficiency include ACTH, cortisol, TSH, free thyroxin (T_4), insulin-like growth factor I (IGF-1), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone (in men) (Vance 2008). Prolactin is also useful for diagnosis, but it must be diluted if the patient presents a large lesion, in order to avoid the “hook effect” and a possible mistaken diagnosis (Vance 2008) (the hook effect may be defined as falsely low values in an immunoassay when an extremely large amount of antigens affects the binding ability of the antibody added).

The medical treatment of choice for patients with NFPA is transsphenoidal surgery (Dekkers et al 2008), a procedure aiming at eradicating the tumor and improving visual field defects, whenever present (Dekkers et al 2007). In a series (N = 109), it was reported that, after surgery, only 21% of patients reached a complete recovery of the visual field and 63% reached partial improvement of the visual field, as well as experienced significant improvement in LH/FSH and TSH deficiencies ($P < 0.01$ e $P < 0.05$, respectively) (Dekkers et al 2006). Complete excision of the tumor is essential to avoid recurrence and prolong survival (Woollons et al 2000). The recurrence-free survival (RFS) rates in five years in post-surgery MRIs were as high as 84% in the absence of residual tumor, but as low as 30% in the presence of residual tumor (Greenman et al 2003). However, the complete resection of the tumor may only be reached in 36% of cases (Ferrante et al 2006).

Before 1992, many patients with NFPA underwent post-surgery radiation therapy (Greenman et al 2003). However, radiation therapy is associated to long-term adverse effects, which include increased incidence of pituitary deficiencies, atrophy of the optical nerve, visual deterioration, increased risk of long-term brain tumors, and neurocognitive or neurophysiological impairment (Dekkers et al 2008)(Ferrante et al 2006). Thus, post-surgery preventive radiation therapy is frequently avoided, being restricted to patients with evidence of remaining tumor increase (Bradley et al 1994)(Turner et al 1999). A NFPA treatment algorithm is shown below (Figure 1-1).

Dekkers et al assessed quality of life (QoL) in 99 adult patients in remission during long-term follow-up after surgical treatment (n = 99) and additional radiation therapy treatment (n = 37) for clinically non-functioning pituitary macroadenoma (NFMA) (Dekkers et al 2006). They concluded that, after these successful treatments for NFMA, QoL decreased considerably in the patients.

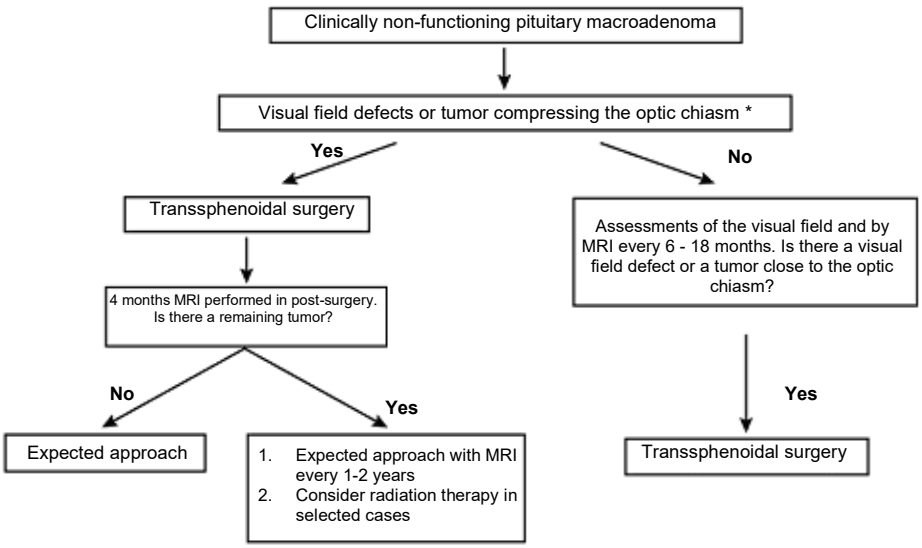


Figure 1-1 Treatment algorithm for clinical NFPA (Dekker et al. 2008)

In addition to the surgical and radiation procedures, two approaches for medical treatment have been investigated: one dopamine-based and one somatostatin-based.

Dopamine, the main catecholamine neurotransmitter in the human central nervous system, controls a number of functions by binding to dopamine receptors on cell surfaces (Pivonello et al 2007). Five different types of dopamine receptors have been identified: D_1, D_2, D_3, D_4, and D_5. These receptors may be subdivided into two groups: those similar to D_1, including D_1 and D_5, and those similar to D_2, including the two D_2 variants (D_{2short} and D_{2long}), in addition to D_3 and D_4. The D_2 receptor is expressed in the anterior and intermediary lobes of the normal pituitary gland, as well as in pituitary tumors that do not secrete prolactin (Pivonello et al

2004). As a result, blocking the D_2 receptor agonist was thought to be effective against NFPAs. Cabergoline is a D_2 receptor agonist with high affinity both to D_2 receptor variants and receptors similar to D_2, D_3, and D_4 (Pivonello et al 2004), in addition to presenting an affinity higher than that of the other D_2 receptor agonist, bromocriptine (see Table 1-2). (Pivonello et al 2007).

Table 1-2 Binding profile of dopamine receptor agonists, cabergoline and bromocriptine (Pivonello et al 2007)

Agent	D_2				D_3		D_4	
	D_{2short}		D_{2long}					
	E_{max} (%)	IC_{50} (nM)	E_{max} (%)	IC_{50} (nM)	E_{max} (%)	IC_{50} (nM)	E_{max} (%)	IC_{50} (nM)
Dopamine	100	350	100	320	100	11	100	100
Bromocriptine	41	4.5	28	3.9	68	4.2	0	>1000
Cabergoline	102	0.53	75	0.41	86	0.78	49	81

E_{max}: maximum efficacy calculated as a percentage of dopamine concentration with maximum efficacy (100%); IC_{50}: concentration leading to 50% inhibition

The results of the treatment with cabergoline for patients with NFPA have not been encouraging or consistent. Additionally, these clinical trials enrolled a small number of patients (see Table 1-3) (Pivonello et al 2004)(Lohmann et al 2001)(Colao et al 2000).

Table 1-3 Summary of Cabergoline Clinical Trials for NFPA

Study	N	Cabergoline Dose	Duration (Months)	Tumor Volume Changes from baseline % of Patients	Visual Field Changes % of Patients
Pivonello et al 2004	9	1 - 3 mg/wk	12	Decrease: 56% Increase: 44%	Improvement: 4/5 (80%)
Lohmann et al 2001	13	0.25 - 1.0 mg/wk	12	Decrease: 54% Unchanged: 38% Increase: 8%	Improvement: 2/9 (22%)
Colao et al 2000	10	5 patients receiving quinagolide, followed by cabergoline: 0.5 mg/wk up to no more than 1.5 mg twice a week; 5 patients received quinagolide alone	6 months with quinagolide, followed by 6 months with cabergoline	Decrease: 0% with quinagolide + cabergoline; Decrease: 20% with quinagolide alone	Improvement: 2/5 (40%) (1 quinagolide + cabergoline;1 quinagolide alone)

Somatostatin is an endogenous peptide that modulates different exocrine and endocrine secretions. There are five known somatostatin receptors: sst 1, 2, 3, 4, and 5, expressed in different tissues under normal physiological conditions. Somatostatin analogues act by binding to these receptors with different affinities (Schmid and Schoeffter 2004). Binding to the receptor triggers a cell signaling cascade that ultimately results in decreased cell activity and hormone secretion inhibition. Somatostatin receptors are strongly expressed in many solid tumors, especially pituitary tumors and neuroendocrine tumors in which hormones are excessively secreted [for example, acromegaly (Freda 2002), GEP/NETs (Modlin 2009), and

Cushing's Disease (Van der Hoek et al 2005), as well as NFPA (Miller et al., 1995; Panetta and Patel, 1995; Taboada et al., 2007)]. Specific somatostatin receptors have been identified in NFPAs cell membranes (de Bruin et al 1992).

Octreotide is a somatostatin synthetic analogue that has shown preferential binding to sst_2 receptor (Colao et al 2008) (See Section 1.2). As with cabergoline, studies on octreotide for the treatment of NFPAs were small and had unsatisfactory results in terms of tumor reduction (see Table 1-4). (Colao et al 1999)(Broson-Chazot et al 1997) (Warnet et al 1997)(Plockinger et al 1994)(Merola et al 1993)(Gasperi et al 1993)(de Bruin et al 1992).

Table 1-4 Summary of Octreotide Clinical Trials for NFPA

Study	N	Octreotide Dose	Duration (Months)	Tumor Volume Changes from baseline % of Patients	Visual Field Changes % of Patients
Colao et al 1999	9	0.3 - 0.6 mg/day SC	6-12	Decreased: 0% Unchanged: 78% Increased: 22%	Not reported
Broson-Chazot et al 1997	16	0.3 mg/day SC	1	Unchanged: 100%	Improved: 50% Unchanged: 38% Worsened: 12%
Warnet et al 1997	29	0.6 mg/day SC	2	7 evaluable patients Decreased: 43% Unchanged: 43% Increased: 14%	22 evaluable patients Improved: 41% Unchanged: 41% Worsened: 18%
Plockinger et al 1994	14	0.3 - 1.5 mg/day SC	3 (pre-surgery)	Decreased: 0% Unchanged: 86% Increased: 14%	Not reported
Merola et al 1993	19	0.15 - 0.3 mg/day SC	1-12	Decreased: 5% Unchanged: 95%	9 evaluable patients Improved: 11% Unchanged: 89%
Gasperi et al 1993	8	0.3 mg/day SC	3-6	Decreased: 0% Unchanged: 75% Increased: 25%	5 evaluable patients Improved: 20% Unchanged: 60% Worsened: 20%
de Bruin et al 1992	4	1.2 mg/day SC	3-6	Unchanged: 100%	Improved: 75% Unchanged: 25%

Combination therapy with dopamine receptor agonist cabergoline and somatostatin analogue octreotide in 10 patients with NFPA produced similar results (Andersen et al 2001). Tumor volume decreased in 6 patients (60%), remained unchanged in 3 (30%), and increased in 1 (10%) patient. Visual acuity improved in 3 (30%) patients and remained unchanged in the other 7 (70%) patients.

A clinical therapy able to control tumor growth and possibly capable of decreasing tumor size would be highly advantageous to patients with NFPA. These therapies could be used pre-surgically to improve surgical result, leading to few patients with remaining tumors, or to control tumor growth or recurrence after surgery, thus avoiding the need for radiation therapy. Another possible benefit related to tumor decrease would be the receovery from hypopituitarism.

1.2 Pasireotide overview (SOM230)

Pasireotide (SOM230) is a new cyclohexapeptide containing the structural elements [(2-amynoethyl) amino carbonyl oxy]-L-proline, phenylglycine, and thyrosine (benzyl). It is a somatostatin analogue with a wider receptor binding profile that may result in a better efficacy in the present indications of octreotide (e.g., acromegaly and gastro-entero-hepatic tumors) and potential efficacy in new indications. Like natural somatostatin and other somatostatin analogues, pasireotide performs its pharmacological activity through somatostatin (stt) receptors binding.

Somatostatin analogues approved for clinical use (octreotide and lanreotide) have high affinity to sst2, with moderate or negligible affinity to the remaining somatostatin receptors. Pasireotide shows a unique high affinity binding profile to four of the five known human somatostatin receptors (sst1, 2, 3, and 5). Compared to octreotide, pasireotide shows a binding affinity 30 to 40-fold higher for sst1 and sst5 receptors, 5-fold higher for sst3 receptors, and comparable for sst2 receptors (see Table 1-5). A detailed summary of the available pre-clinical data is provided in the Investigator's Brochure. The lanreotide binding profile is similar to that of octreotide (Table 1-5).

Table 1-5 Binding profile of octreotide, pasireotide, and lanreotida in hsst 1-5. The results are mean values ± IC_{50} SEM shown in mmol/L. Adapted from Bruns et al 2002

Compound	sst1	sst2	sst3	sst4	sst5
Octreotide acetate (SMS 201-995)	280 ± 80	0.38 ± 0.08	7.1 ± 1.4	>1000	6.3 ± 1.0
Lanreotide	180 ± 20	0.54 ± 0.08	14 ± 9	230 ± 40	17 ± 5
Pasireotide (SDZ 227-230)	9.3 ± 0.1	1.0 ± 0.1	1.5 ± 0.3	>100	0.16 ± 0.01
IC_{50} Ratio: octreotide acetate / pasireotide	30	0.38	4.7	--	39.4
IC_{50} Ratio: lanreotide / pasireotide	19.4	0.54	9.3	--	106

There are two pasireotide formulations under complete clinical development, i.e., SC (subcutaneous) and IM (intramuscular) LAR (long-acting release) formulations. A detailed summary of the available pre-clinical data is provided in the Investigator's Brochure.

Pasireotide has been well tolerated when administered subcutaneously (SC) to healthy volunteers as continuous infusion for seven days [CSOM230B2108] with total daily doses of up to 2025 µg. Subcutaneous pasireotide has been subsequently evaluated in two phase II studies with 45 patients with metastatic carcinoid tumors and carcinoid syndrome symptoms [CSOM230B2202] and in 39 patients with Cushing's Disease [CSOM230B2208] at doses of up to 1200 µg BID. SC pasireotide has been well tolerated, with gastrointestinal events as the most common adverse events (AEs). Hyperglycemia has also been seen and appeared more marked in patients with history of hyperglycemia or diabetes mellitus. However, blood glucose in these patients was easily controlled by adjusting oral anti-hyperglycemic agents or, in some cases, by adding insulin. Details and available data from these studies [CSOM230B2202], [CSOM230B2208] are described in the Investigator's Brochure for SC pasireotide.

Efficacy and safety data are available from a Phase II study [CSOM230B2201] in patients with recurrent, persistent or *de novo* acromegaly. After initial treatment with SC octreotide 100 µg TID for 28 days, patients received pasireotide 200 µg SC BID, 400 µg SC BID, and 600 µg SC BID randomly for 28 days each (total period of the study: 16 weeks). Overall, 60 patients received treatment with pasireotide during this study. Regarding the previous medical treatment for acromegaly at study enrollment, 67% of patients received previous therapy with somastotatin analogue, 10% received medical treatment for acromegaly, but did not receive somatostatin analogues (no treatment with somatostatin analogue), and 23% of patients experienced *de novo* disease. Sixty patients were evaluated for safety. All dosage levels of 200, 400, and 600 µg of SC pasireotide BID were, usually, well tolerated. The adverse events were predominantly gastrointestinal, including nausea (23%), diarrhea (20%), and abdominal pain (10%), and mild or moderate in severity. Overall, the events resolved spontaneously during continuous treatment. Other AEs occurring with a frequency ≥ 5% were headache (12%), increased glycated hemoglobin (7%), dizziness (5%), bronchitis (5%), nasopharyngitis (5%), and back pain (5%). For 13 (22%) of the 60 patients in the safety population, AEs of metabolism and nutritional disorders were reported, including diabetes mellitus (4 patients), non-insulin dependent diabetes mellitus (2 patients), impaired glucose tolerability (2 patients), hyperglycemia (1 patient), hypoglycemia (2 patients), hypocalemia (1 patient), and hyponatremia (1 patient). Eight of these patients had a pre-existing history of diabetes or glucose intolerability at baseline. For five (8%) patients, an increase in blood glucose was reported. These events did not require treatment or were effectively controlled by changes in the anti-hyperglicemic medication. Only one patient, who had pre-existing diabetes at baseline, was discontinued from the 3-month treatment with pasireotide due to worsening of glycemic control. Glycated hemoglobin (SD) (n = 58) was within the upper limit of normal at baseline at 6.01% (0.57), increasing to 6.45% (0.84) during the 12-week treatment period with pasireotide. This change was not significant. There were no reports of deaths or reported serious AEs considered related to pasireotide during this study.

Gallbladder ultrasound scans showed that 3.7% of patients with normal gallbladder ultrasounds at baseline had gallstones after treatment with pasireotide. Colelithiasis is a known side effect associated to the therapy with somatostatin analogues, which is normally asymptomatic. Long-term data on gallbladder abnormalities related to pasireotide are not yet available.

Other details and data available from the study [CSOM230B2201] are described in the Investigator's Brochure for SC pasireotide.

Pasireotide LAR was evaluated in two further studies, one in healthy volunteers [CSOM230C2101] and one in patients, which is still ongoing [CSOM230C2110]. Preliminary data from the study in healthy volunteers [CSOM230C2101] evaluating single IM pasireotide LAR doses of up to 60 mg (N = 5 per cohort) show that pasireotide LAR was well tolerated and that the adverse events seen are comparable to those seen with octreotide LAR. The most common adverse event was diarrhea, which was sometimes associated to abdominal pain and/or flatulence. Gastrointestinal events were mild to moderate in severity. Approximately half of the subjects reported transient mild pain at the injection site. Two volunteers who received a 60 mg dose experienced mild increases in fasting blood glucose (< 123 mg/dL), with all values returning to normal 28 days after the LAR injection.
Pasireotide LAR pharmacokinetics was evaluated in healthy volunteers after a single IM injection of 40 or 60 mg. Pasireotide exposure was dose-proportional, with long-acting release phase C_{max} of 9.6 ± 5.1 ng/mL and 15.8 ± 3.3 ng/mL for 40 and 60 mg doses, respectively. Simulation with multiple doses suggested that this form of LAR is appropriate for monthly dosing (every 28 days). The simulated residual concentrations at steady-state ($C_{residual,ss}$) were 5.5 and 11.5 ng/mL at 40 and 60 mg, respectively.

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

Pasireotide LAR is being tested in a study in patients, which is still ongoing [CSOM230C2110]. It is a Phase I, multicenter, open-label, randomized study to evaluate the pharmacokinetics, safety, and tolerability of monthly doses (dosing every 28 days) of 20, 40, and 60 mg of pasireotide LAR as depot IM injections administered to patients with acromegaly and patients with 1carcinoid disease. Thirty-five patients with acromegaly and 42 carcinoid patients were enrolled (approximately 10 patients per dose cohort by indication). Patients in this study receive pasireotide, given as depot intragluteal IM injection once every 28 days, for 3 months. The preliminary efficacy, safety, and clinical PK/PD analysis results are available for 35 patients with acromegaly, including 10, 12, and 13 patients in dose groups of 20, 40, and 60 mg of pasireotide LAR. The efficacy results are shown on Table 1-6.

Table 1-6 Number (percentage) of responders among patients with acromegaly with mean GH level ≤ 5 mg/mL and IGF-1 level within normal limits compared to controls of equivalent age and gender after three monthly IM injections of 20 mg, 40 mg, or 60 mg of pasireotide LAR formulation – Study [CSOM230C2110]

Dose	20 mg (N = 10)	40 mg (N = 12)	60 mg (N = 13)
Overall *	4 (40%)	4 (36%)	7 (54%)
Mean GH < 2.5 µg/L **	5 (50%)	6 (50%)	7 (54%)
IGF-1 within normal limits compared to controls of equivalent age and gender	5 (50%)	7 (64%)	8 (62%)

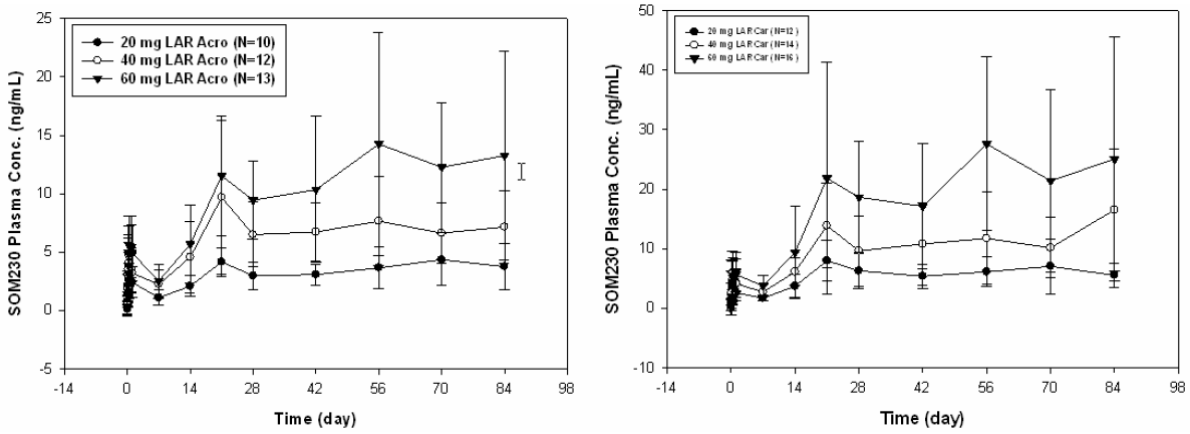
* Patients with mean GH < 2.5 µg/L and IGF-1 within normal limits compared to controls of equivalent age and gender
** Mean GH was obtained at -0 min. (pre-dose) and 30, 60, 90, and 120 minutes post-dose

This study also showed that pasireotide LAR was generally well tolerated, and that the most common adverse events were gastrointestinal and mild in intensity. Although pre-clinical or clinical trials have not shown any specific cardiac toxicity issue related to pasireotide, a complete clinical QT/QTc evaluation was performed in healthy volunteers [CSOM230B2113]. In Part I of the study, 900 µg to 2100 µg doses of pasireotide were investigated, after which the maximum tolerated dose (MTD) of pasireotide was defined as 1950 µg SC BID. The MTD was then used as the pasireotide dose in Part II of the study (i.e., a three-way crossover design using moxifloxacin, placebo, and 1950 µg of SC pasireotide BID). The effect of pasireotide (at the MTD) on the QTcF interval was shown. This effect was based on the upper limit of the 1-sided 95% CI for the difference compared to placebo in the QTcF change from baseline of > 10 ms, in one or more timepoints. Pasireotide and moxifloxacin showed maximum effect 2 hours after dosage (QTcF change of 17.5 ms and 8.5 ms from baseline compared to placebo, respectively). Subjects receiving pasireotide also showed a HR decrease within 0 to 4 hours post-dose (maximum change versus baseline of 10.7 bpm). The appropriate ECG monitoring of patients assigned to pasireotide LAR arms is implemented in the protocol.

Other detailed information on clinical efficacy and safety of pasireotide LAR may be found in the Investigator's Brochure.

Mean concentration (SD) profiles over time for pasireotide are shown on Figure 1-2. PK analysis showed that steady state was reached with three montly injections of pasireotide LAR. Residual (pre-dose) plasma concentrations of pasireotide on days 28, 56, and 84 indicated that PK exposures were almost dose-proportional. The PK exposure ratio between the study populations was healthy volunteers : patients with acromegaly : patients with carcinoid tumors = ~ 1 : 1 : 2 for pasireotide LAR, similarly to the proportion for SC pasireotide.

Figure 1-2 **Mean plasma concentration (SD) profiles over time for pasireotide in patients with acromegaly (left panel) and carcinoid patients (right panel) after three monthly IM injections of 20 mg, 40 mg, or 60 mg of pasireotide LAR [CSOM230C2110]**



In summary, results from clinical trials with pasireotide currently available indicate that it is a safe and effective treatment in patients with acromegaly. However, to date, there are no clinical data available from clinical trials in patients with clinically non-functioning pituitary adenomas.

1.3 Human experience

Although the SC and LAR pasireotide formulations have not been tested in patients with NFPA, both formulations were tested in healthy volunteers [CSOM230C2101] and in patients with acromegaly {[CSOM230B2103], [CSOM230B2101], [CSOM230B2101E], [CSOM230C2110], and [CSOM230C2305]}, with carcinoid tumors {[CSOM230B2202], [CSOM230C2110] and [CSOM230C2303]}, and with Cushing's Disease {[CSOM230B2208] and [CSOM230B2305]}. To date, clinical safety and efficacy data available from these studies suggest that pasireotide is well tolerated and has positive activity on the treatment of patients with acromegaly, Cushing's Disease, and carcinoid tumor. Studies [CSOM230B2305], [CSOM230C2305] and [CSOM230C2303] are ongoing.

1.3.1 Clinical efficacy and safety of pasireotide LAR

The pasireotide LAR formulation was studied in three studies: [CSOM230C2101], in healthy volunteers, [CSOM230C2110], in patients with acromegaly and carcinoid tumors, and [CSOM230C2305] – the registry program currently ongoing in patients with acromegaly.

Study [CSOM230C2101], evaluating single intramuscular (IM) doses of 40 and 60 mg of pasireotide LAR (N = 5 per dose cohort) in healthy volunteers showed that pasireotide LAR was well tolerated, and that there was no difference in the frequency of AEs seen between pasireotide LAR and octreotide LAR. The most common AE was diarrhea, which was sometimes associated to abdominal pain and/or flatulence. Gastrointestinal events were mild or moderate in intensity. Approximately half of the subjects reported mild transient pain at the injection site. Two volunteers on the 60 mg dose showed mild increases in fasting blood glucose (< 123 mg/dL), with all values returning to normal 28 days after the LAR injection.

Study [CSOM230C2110] evaluated single IM pasireotide LAR doses of up to 60 mg in patients with acromegaly or carcinoid disease. The preliminary results of the clinical efficacy, safety, and pharmacokinetics/pharmacodynamics (PK/PD) analysis are available for 35 patients with acromegaly, including 10, 12, and 13 patients in dose groups of 20, 40 and 60 mg of pasireotide LAR, respectively, and are summarized on Table 1-7.

Table 1-7 Number (percentage) of responders among patients with acromegaly with a GH mean level ≤ 2.5 ng/mL and IGF-1 level within normal limits for controls of equivalent age and gender after three monthly IM injections of 20 mg, 40 mg, or 60 mg of pasireotide LAR formulation (2b) [CSOM230C2110]

Dose	20 mg (N = 10)	40 mg (N = 12)	60 mg (N = 13)
Overall *	**4 (40%)**	**4 (36%)**	**7 (54%)**
Mean GH < 2.5 ng/mL **	5 (50%)	6 (50%)	7 (54%)
IGF-1 within normal limits for controls of equivalent age and gender	5 (50%)	7 (64%)	8 (62%)

* Patients with mean GH < 2.5 ng/mL and IGF-1 within normal limits for controls of equivalent age and gender

** GH was collected at -30 and 0 min. (pre-dose). The mean of these first samples was calculated. The 4 remaining samples were collected post-dose and were not included in the mean calculation.

This study has also shown that pasireotide LAR was generally well tolerated, and that the most common adverse events seen were gastrointestinal and mild in intensity. Although pre-clinical or clinical trials have not revealed any specific cardiac toxicity issue related to pasireotide, a complete clinical evaluation of QT/QTc was performed in healthy volunteers [CSOM230B2113]. In Part I of the study, 900 µg to 2100 µg doses of pasireotide were investigated, after which the maximum tolerated dose (MTD) of pasireotide was defined as 1950 µg SC BID. The MTD was then used as the pasireotide dose in Part II of the study (i.e., a 3-way crossover design using moxifloxacin, placebo and 1950 µg of SC pasireotide BID). The effect of pasireotide (at the MTD) on the QTcF interval was shown. This effect was based on the upper limit of the 1-sided 95% CI for the difference compared to placebo in QTcF

change from baseline of > 10 ms, in one or more timepoints. Pasireotide and moxifloxacin showed maximum effect 2 hours post-dose (QTcF change of 17.5 ms and 8.5 ms from baseline compared to placebo, respectively). Subjects receiving pasireotide also showed a HR decrease within 0 to 4 hours post-dose (maximum change versus baseline of 10.7 bpm). The appropriate monitoring of the ECG of patients assigned to pasireotide LAR arms is implemented in the protocol. Other detailed information on clinical efficacy and safety of pasireotide LAR may be found in the [Investigator's Brochure].

Study [CSOM230C2305] is evaluating the efficacy and safety of pasireotide LAR in patients with acromegaly (without medical treatment) compared to octreotide LAR. This study is still ongoing.

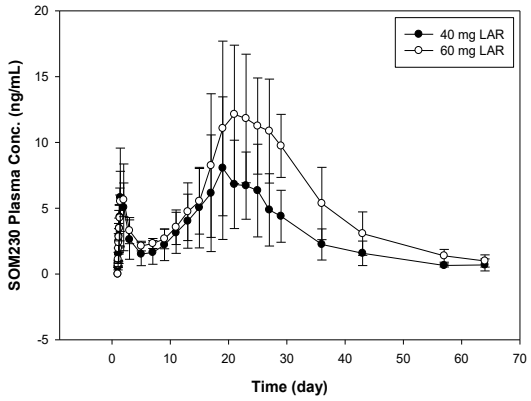
Other detailed information on clinical efficacy and safety of pasireotide LAR may be found in the [Investigator's Brochure].

1.3.2 Pasireotide clinical pharmacokinetics

1.3.2.1 Single pasireotide LAR injection in healthy volunteers

In healthy volunteers [CSOM230C2101], single IM injections of pasireotide LAR 40 mg and 60 mg showed types of long-acting release concentrations compared to time profiles characterized by an initial outburst on day 1, followed by a long-acting release (Figure 1-3).

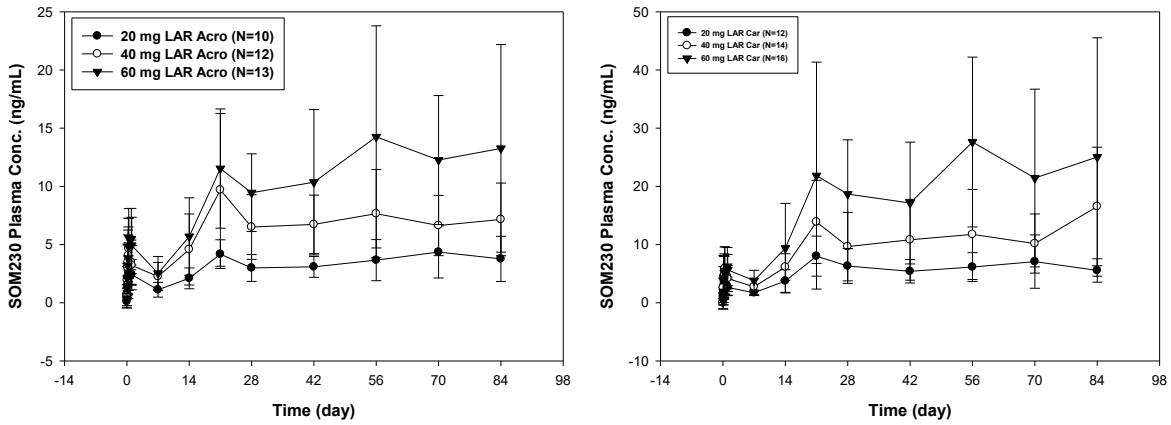
Figure 1-3 **Mean plasma concentration (SD) profiles over time for pasireotide after a single IM injection of 40 mg (N = 5) or 60 mg (N = 5) of pasireotide LAR formulation in healthy volunteers [CSOM230C2101]**



1.3.2.2 Multiple monthly injections of pasireotide LAR in patients with acromegaly and carcinoid tumors

Pasireotide LAR was tested in patients with acromegaly and patients with carcinoid tumors receiving IM injections, three times a month, in dosage levels of 20, 40, and 60 mg in a Phase I study [CSOM230C2110]. The mean concentration (SD) profiles over time for pasireotide are shown on Figure 1-4. The PK analysis showed that steady state was reached within three monthly injections of pasireotide LAR. Residual plasma concentrations (pre-dose) of pasireotide on days 28, 56, and 84 indicated that the PK exposures were almost dose proportional. The PK exposure ratio among the study populations was healthy volunteers : patients with acromegaly : patients with carcinoid tumors = ~ 1 : 1 : 2 for pasireotide LAR, similarly to the proportion for SC pasireotide.

Figure 1-4 **Mean plasma concentration (SD) profiles over time for pasireotide in patients with acromegaly (left panel) and patients with carcinoid tumor (right panel) after three monthly IM injections of 20 mg, 40 mg, or 60 mg of pasireotide LAR [CSOM230C2110]**



2 Study rationale / purpose

The purpose of this phase II, prospective, multicenter, open-label, single-arm study is to evaluate the efficacy and safety of pasireotide LAR in patients with clinically non-functioning pituitary adenomas (NFPAs).

Pituitary adenomas seem to be associated to intact transmembrane G protein-coupled somatostatin receptors and to the increased expression of the vascular endothelial growth factor (VEGF), which is correlated to vascularization and to the increase in tumor proliferation (Onofri et al 2006)(Turner et al 2003). Particularly, NFPAs showed a significantly higher expression of VEGF protein (3.2 times, $P < 0.05$) than normal pituitary glands (McCabe et al 2002).

Miller et al. showed SSTR1, 2, and 5 expression in clinically non-functioning pituitary adenomas (Miller et al., 1995). Panetta and Patel have also studied the expression of SSTRs in the mRNA from secretory and clinically non-functioning adenomas, observing SSTR1 and SSTR2 in most of adenomas, while SSTR3, 4 and 5 were expressed in approximately half of the adenomas (Panetta and Patel, 1995).

Another study revealed that the most expressed receptor subtype was sst3, followed by sst2 (which is the most highly expressed receptor in GH secretory adenomas), while sst1, sst4, and sst5 transcripts were detected only in a few tumors (Taboada et al. 2007).

Somatostatin and its analogues seem to inhibit the proliferation of pituitary adenomas interacting with one or more of its G protein-coupled transmembrane receptors: sst 1, sst 2, sst 3, sst 4, and sst 5 (Zatelli et al 2006). A NFPA in vitro study showed that sst 1 selective agonists inhibit secretory activity and cell viability, sst 2 selective agonists inhibit secretion, but not cell viability, and sst 5 selective agonists do not affect secretory activity, but promote cell viability (Zatelli et al 2004). Another study conducted using the same SSTR selective analogues showed a decrease in cell viability in 3 of the 10 NFPAs treated in vitro with SSTR1 analogue, in 4/10 NFPAs incubated with SSTR2 selective analogue, and in 4/10 adenomas exposed to a SSTR5 agonist (Gruszka et al., 2006).

Natural somatostatin (binding all ssts) and the sst3 and sst2 selective analogues inhibited chromogranin A (CgA) and alpha subunit concentration in vitro in cell culture medium (Pawlikowski et al. 2007). CgA inhibition is also correlated to sst5 expression (Pawlikowski et al. 2007).

Padova et al. showed that SSTR2 and SSTR5 selective analogues decreased cell viability in 8/13 and 10/13 of NFPAs exposed to these in vitro peptides, respectively. This inhibitory effect of a compound tested for the number of viable cells in an adenoma culture reflects a probable antitumoral effect of this peptide (Colao et al 2008)(Padova et al 2008).

Pasireotide LAR (SOM230) is a new somatostatin analogue with properties similar to natural somatostatin and, specifically, high affinity and functional activity to sst 1, sst 2, sst 3, and sst 5 (Bruns et al 2002)(Schmid et al 2004). Pasireotide has been shown to inhibit GH and prolactin secretion from in vitro pituitary adenomas (Hofland et al 2004)(Murray et al 2004), in vitro ACTH, (Batista et al 2006), and in vivo GH/IGF-1 (Weckbecker et al 2002)(Fedele et al 2007). Additionally, pasireotide inhibited the proliferation of cells stimulated by endothelial VEGF (Adams et al 2004).

A pre-clinical trial showed that pasireotide avoids NFPA cell viability by inhibiting VEGF secretion, which indicates that this multireceptor SSTR agonist may be useful as medical therapy for NFPA (Zatelli et al 2007).

Pasireotide LAR was tested in clinical trials in healthy volunteers [CSOM230C2101] and in 2 populations of patients (i.e., acromegaly and carcinoid disease [CSOM230C2110]). However, there are no previous reports about the clinical use of pasireotide LAR for NFPAs.

Based on these findings and on the need of a medical therapy that may be used pre-surgically to improve surgical results, leading to less patients with remaining tumors, or to control tumor growth or recurrence after surgery, avoiding the need for radiation therapy, pasireotide LAR may be a good medical option for treatment, both as pre-surgical therapy and in the control of post-surgical tumor growth.

3 Objectives

3.1 Primary objective

- To evaluate the efficacy of pasireotide LAR in the proportion of patients with clinically non-functioning pituitary adenomas (NFPAs) who responded to treatment.

3.1.1 Primary objective endpoint

- Proportion of patients with NFPA reaching a decrease in tumor volume of at least 20% after the 24-week treatment with pasireotide LAR.

3.2 Secondary objectives

- To evaluate the effect of pasireotide LAR in mean tumor volume variation between baseline and treatment weeks 4, 12, 24, 48, 72, and 96.
- To evaluate the effect of pasireotide LAR in mean percent tumor volume variation between baseline and treatment weeks 4, 12, 24, 48, 72, and 96.
- To evaluate the effect of pasireotide LAR in the proportion of patients reaching tumor volume decrease of at least ≥ 20% after 4, 12, 48, 72, and 96 weeks of treatment.
- To evaluate the effect of pasireotide LAR on time to tumor response.
- To evaluate the effect of pasireotide LAR on the disease-related symptoms *
  * Disease-related symptoms to be evaluated: headache, visual disorders, fatigue, decreased libido, erectile dysfunction (for men only), menstrual irregulatiry or interruption (only for non-menopausal women).
- To evaluate the effect of pasireotide LAR on the pituitary function on weeks 4, 12, 24, 48, 72, and 96.
- To evaluate the effect of pasireotide LAR on the alpha subunit levels on weeks 4, 12, 24, 48, 72, and 96.
- To evaluate the overall safety and tolerability of pasireotide LAR.
- For the extension phase: duration of response for patients considered as responders (i.e., patients reaching a tumor volume decrease of at least 20% compared to the initial tumor volume).
- To evaluate the percentage of patients remaining with stable tumor volume during the study.

3.2.1 Secondary objective endpoints

The secondary variables are:

- Mean change in tumor volume evaluated by pituitary MRI between baseline and weeks 4, 12, 24, 48, 72, and 96.
- Percent change in tumor volume evaluated by pituitary MRI between baseline and weeks 4, 12, 24, 48, 72, and 96.
- Proportion of patients reaching tumor volume decrease of at least ≥ 20% after 4, 12, 48, 72, and 96 weeks of treatment.

- Time to treatment response for treatment responders, defined as the time from the date of the first injection to the first evaluation in which the patient reached a tumor volume decrease of at least ≥ 20%.
- Change in grading score of disease-related symptoms between baseline and weeks 4, 12, 24, 48, 72, and 96.
- Incidence of pituitary hormone dysfunction at baseline and on weeks 4, 12, 24, 48, 72, and 96.
- Proportion of patients reaching alpha subunit decrease of at least 50% on weeks 4, 12, 24, 48, 72, and 96.
- Proportion of patients reaching alpha subunit normalization on weeks 4, 12, 24, 48, 72, and 96.
- Percentage of adverse events with CTC grade ≥ 3 during treatment with pasireotide LAR.
- Percentage of patients with at least one adverse event with CTC grade ≥ 3.
- Incidence of all adverse events, incidence of abnormal lab values, and summary of laboratory evaluations.
- For the extension phase: among patients who had been considered as responders (i.e., patients reaching a tumor volume decrease of at least 20% compared to initial tumor volume), to evaluate the number and proportion of patients who remained responsive during the extension phase treatment (according to the magnetic resonance imaging evaluations on weeks 48, 72, and 96).
- To evaluate the percentage of patients remaining with stable tumor volume during the study, i.e., patients who mantained tumor volume variation lower than 20% compared to baseline tumor volume (according to magnetic resonance imaging evaluations on weeks 24, 48, 72, and 96).
- If applicable, to evaluate whether there was a difference in response among patients on 40 and 60 mg doses of pasireotide LAR.

[redacted]

4 Study design

A phase II, open-label, single-arm, prospective, multicenter study to evaluate the efficacy and safety of pasireotide LAR in adult patients with NFPA.

Eligible patients will receive 60 mg of pasireotide LAR every 28 ± 3 days for 24 weeks, during the Main Phase of the study. The study is complemented by an extension. At the discretion of the treating physician, patients who benefit from the treatment with pasireotide LAR will be offered the opportunity to enter an Extension Phase, in which they will continue to receive pasireotide LAR 60 mg at 4-week intervals (± 3 days) for up to 2 years (Table 7-2), or until pasireotide or other effective therapy is commercially available, or until clinical benefit is no longer seen (whichever occurs first). Dose decreases until 40 mg will be allowed, based on safety issues (see Section 6.4.2). In case of rapid deterioration of the visual field or sudden visual loss, the patient will be discontinued from the study.

During the Main Phase of the study, visits will be performed every 28 ± 3 days. There will be two additional safety visits: Visit 3 and Visit 6.

The sella turcica MRI will be performed during the screening period (baseline imaging). The follow-up MRIs will be performed on weeks 4, 12, and 24 in the Main Phase and on weeks 48, 72, and 96 in the Extension Phase, and must be performed within 7 days of the appropriate visit. Enhancement with gadolinium contrast will be used to obtain the MRI.

The MRIs will be submitted to a central evaluator. In order to ensure consistency in all participating sites, MRIs must be performed and processed according to the guidelines of the central reading facility, which will be distributed to the sites before study start.

The visual field evaluations will be performed during the screening period (they will be considered as baseline data) and then every 4 weeks ± 3 days thereafter.

Symptoms and potential AEs will be evaluated on all visits. Safety-related tests will be performed as described on Table 7-1 and Table 7-2 (Visits and evaluations schedule for the Main Study).

Alpha subunit and pituitary hormone levels will be evaluated during the screening period (and will be considered as baseline data), as well as on Weeks 4, 12, and 24 in the Main Phase and on weeks 48, 72, and 96 in the Extension Phase.

[redacted]

The gallbladder ultrasound will be evaluated in the screening period and within 7 days of Visit 10 (Week 24). In the Extension Phase, it will be evaluated on weeks 48 and 96.

After the Main Phase of the study (first 24 weeks of treatment), patients deriving benefit from pasireotide LAR will be offered the opportunity to continue receiving pasireotide LAR, based on the physician's evaluation and the patient's wishes. This will be called study Extension Phase. The study design and a Main Phase and Extension Phase scheme are shown on Figure 4-1 **and Figure 4-2,** respectively.

Figure 4-1 Scheme of NFPA Study with Pasireotide LAR: Main Phase

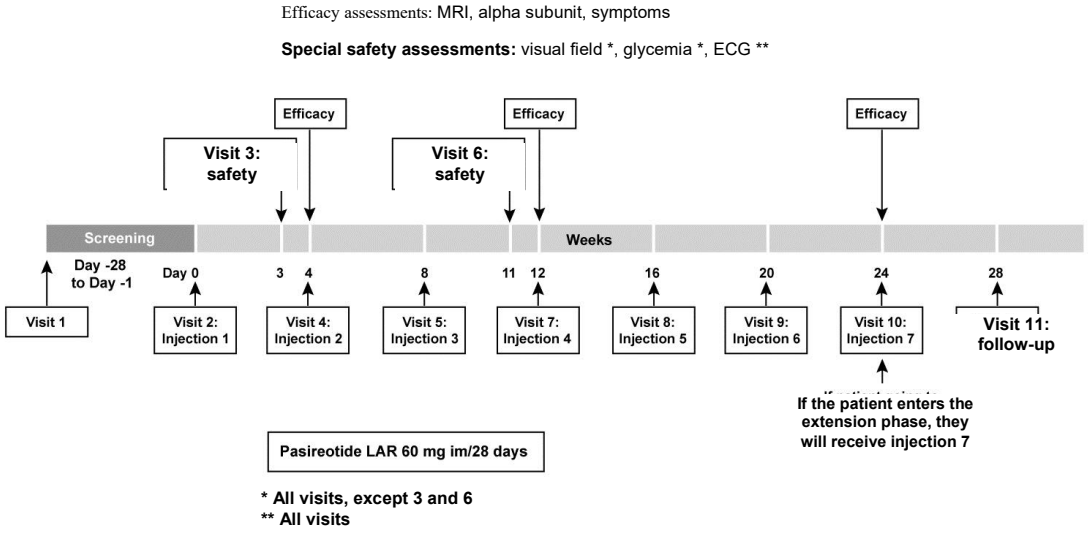
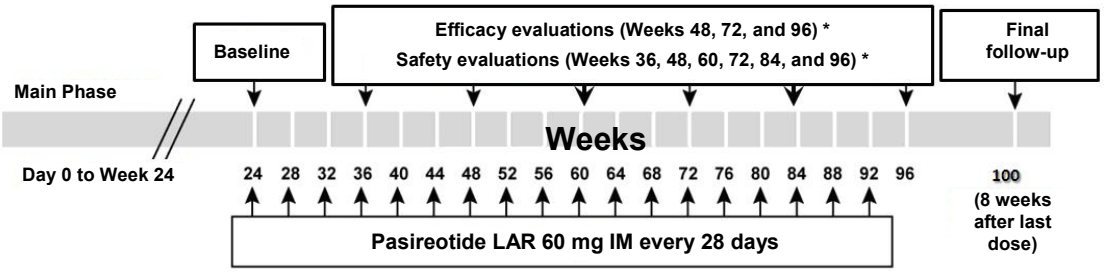


Figure 4-2 Scheme of NFPA Study with Pasireotide LAR: Extension Phase



*** For details of efficacy and safety evaluations, see Table 7-2.**

5 Population

The population for this study consists of adults diagnosed with NFPA who did not receive any other previous therapy (treatment-naïve) for the disease. Due to the difficulty to evaluate changes in tumor volume in microadenomas, and also because they can be mistakenly diagnosed as incidentalomas, only patients with macroadenomas (≥ 1 cm) will be enrolled in the study. A total of 23 patients in 10 - 13 sites will be enrolled in this single-arm open-label study.

Inclusion / exclusion criteria

The investigator or his/her designee must ensure that enrollement in the study is offered to all patients meeting the inclusion and exclusion criteria.

5.1 Inclusion criteria

1. Male or female patients ≥ 18 years old.
2. Patients with clinically non-functioning pituitary macroadenomas ≥ 1 cm.
3. Patients without previous treatment for NFPA.
4. Patients with Eastern Cooperative Oncology Group (ECOG) Performance status of 0 to 1.
5. Written Informed Consent Form obtained before any screening procedure.

5.2 Exclusion criteria

1. Patients requiring surgical intervention for relief of any sign or symptom related to tumor compression.
2. Previous pituitary surgery.
3. Previous medical treatment for pituitary tumor.
4. Patients who received pituitary radiation within 10 years before the enrollment visit (Visit 2).
5. Prolactin (PRL) levels > 100 ng/mL. (PRL evaluation must be performed with diluted samples in order to ensure prevention of the "hook effect").
6. Patients with optic chiasm compression, causing clinically significant acute visual field defects.
7. Diabetic patients whose blood glucose is poorly controlled, as proven by HbA1C > 8%. Patients with known history of fasting glucose impairment or diabetes mellitus with HbA1c < 8% may be enrolled; however, blood glucose and antidiabetic treatment must be closely monitored throughout the study and adjusted as required.
8. Patients with known gallbladder or bile duct disease, or acute or chronic pancreatitis (patients with asymptomatic colelithiasis and asymptomatic dilation of the bile duct may be enrolled).
9. Patients with abnormal coagulation (increased PT or APTT 30% above normal limits) or patients who have received antiacoagulants that affect PT (prothrombin time) or APTT (activated partial thromboplastin time).
10. Patients with congestive heart failure (NYHA Class III or IV), unstable angina, persistent ventricular tachycardia, ventricular fibrillation, advanced cardiac block, or history of acute myocardial infarction within 24 weeks before the enrollment visit (Visit 2).
11. Screening (Visit 1) or baseline (pre-dose, Visit 2) QTcF > 450 msec.
12. Patients with history of syncope or family history of idiopathic sudden death.

13. Patients with persistent or clinically significant cardiac arrhythmias.
14. Patients with Torsades de Pointes risk factors, such as uncorrected hypocalemia, uncorrected hypomagnesemia, heart failure, clinically significant / symptomatic bradycardia, or high degree AV block.
15. Patients with concurrent disease(s) that might prolong the QT interval, such as autonomous neuropathy (caused by diabetes or Parkinson's disease), HIV, cirrhosis, uncontrolled hypothyroidism, or heart failure.
16. Patients on medication(s) known to prolong the QT interval.
17. Patients with liver disease or history of liver disease, such as cirrhosis, active chronic hepatitis B and C, or persistent chronic hepatitis, or patients with ALT and/or AST > 2 x ULN, total blood bilirubin > 1.5 x ULN, and serum albumin < 0.67 x LLN.
18. Patients with blood creatinine > 2.0 x ULN.
19. Patients with WBC < 3 x 10^9/L; Hgb < 90% LLN; PLT < 100 x 10^9/L.
20. Patients with any current or previous medical condition that, in the investigator's opinion, might interfere in the study conduction or evaluation of the study results.
21. Patients with history of immunological impairment, including positive result for HIV tests (ELISA and Western blot). HIV tests will not be required; however, previous medical history will be analyzed.
22. Patients with known hypersensitivity to somatostatin analogues or any other pasireotide LAR compound.
23. Patients with active malignant disease within the last five years (except for basal cell carcinoma or in situ cervix carcinoma).
24. Patients with presence of uncontrolled, acute suspected, or active chronic infection.
25. Pregnant or breastfeeding patients, or patients of childbearing potential who do not adopt a clinically acceptable contraceptive method. If a woman is participating in the study, then one contraceptive method will be sufficient (pill or diaphragm), and the partner must use condoms. If an oral contraceptive is used in addition to condoms, the patient must have adopted this method at least two months prior to enrollment in the study, and must agree to continue to use it throughout the study, and for three months after the end of the study. Sexually active male patients are required to use condoms during the study and for three months after the end of the study, as a precautionary measure (the available data do not suggest any increase in reproductive risk with the study drugs).
26. Study participants on the investigational drug 30 days prior to the enrollment visit (Visit 2). Patients must have recovered from all side effects from other investigational therapies.

27. Patients with history of non-compliance to medical regimens, or patients considered potentially unsafe, or any circumstance at the time of study enrollment that might prevent the completion of the entire study or the follow-up required.
28. Patients with history or recurrence of undue use / abuse of alcohol or drugs within 12 months previous to visit 1 (screening).
29. Presence of Hepatitis B surface antigen (HBsAg).
30. Presence of Hepatitis C antibody screen (anti-HCV).
31. Patients who had a major surgery / surgical therapy for any cause within 4 weeks before randomization.
32. Patients with confirmed hypothyroidism, hypoadrenalism and hypogonadism (except for physiological andropause and menopause), unless appropriately treated with stable doses of hormone replacement therapy for at least 3 months before study entry.
33. Patients on growth hormone replacement therapy.
34. Patients with uncontrolled cardiovascular, renal or metabolic disorders.
35. Patients with severe neurological or psychiatric disorders.
36. Patients with contraindications to MRI such as, for example, (but not limited to): brain aneurysm clips, internal wiring of cardiac pacemaker and temporary pacemaker, cochlear implants, hearing devices containing internal non-removable parts, Swan-Ganz catheter, aortic balloon, Endovascular Graft Zenith AAA, and other potential contraindications related to ferromagnetic materials identified in the patient's interview.

6 Treatment

6.1 Investigational drug

The study drug is pasireotide LAR (long-acting release), depot IM injection.

Pasireotide LAR excipients include: mannitol, sodium carmellose (sodium carboxymethyl cellulose), poloxamer 188, and water for injection.

6.1.1 Known untoward effects of the study drug / treatment

Refer to the Investigator's Brochure for further information.

6.1.2 Supply

Novartis will provide the investigational drug pasireotide LAR, as 20 and 40 mg of powder in vials and 2 mL of vehicle in ampoules (for reconstitution), provided in boxes.

The medication labels will meet the Brazilian legal requirements and will be printed in Portuguese. They will not contain patient information. The storage conditions of the study drug will be described in the medication label.

6.1.3 Preparation and storage

Pasireotide LAR must be prepared as described on Table 6-1:

Table 6-1 Handling and preparation of pasireotide LAR dose

Dose (mg)	Volume to be injected
60 mg	1 20 mg vial + 1 40 mg vial + 2 mL of vehicle; total volume to be injected
40 mg	1 40 mg vial + 2 mL of vehicle: total volume to be injected

The doses must be prepared and administered immediately after preparation. For additional instructions on the handling and preparation of pasireotide LAR doses, refer to [Post-Text Supplement 3].

The drug supplies must be kept in an appropriate and safe area (for example, a locked cabinet) and stored according to the conditions specified on the drug labels. The receipt and dispensing of the study drug must be recorded by an authorized person at the Investigator's site. The Investigator must keep an accurate shipment and dispensing record of the study drug in a drug accountability log, and a copy of this form will be provided to Novartis at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. Unless specifically instructed by Novartis, the Investigator must not destroy the labels of any drug or any partially used and unused drug supply. Any partially used ampoule must not be reused in another injection.

6.2 Patient numbering

Each study patient is uniquely identified by a 6-digit patient number, which is a combination of the 3-digit site number and the 3-digit subject number. The site number is assigned by Novartis to the investigational site. Upon signature of the Informed Consent Form, the investigator or his/her designee assigns a number to the subject. Once assigned to a patient, the number will not be reused. If the patient cannot start treatment for any reason, this reason will be entered in the Screening Record electronic Case Report Form (eCRF), and the patient's demographics will be entered in the Demographics eCRF.

The Informed Consent Form must be obtained before performing any test to determine the patient's eligibility.

6.3 Treatment assignment

This is a single-arm open-label study. All patients will receive pasireotide LAR 60 mg every 28 ± 3 days for 24 weeks. In case of problems related to drug tolerability, the treatment dose may be adjusted (see Section 6.6.2) or the study medication may be discontinued (see Section 6.4.2).

6.4 Patient treatment

All pasireotide LAR injections must be administered only by a medical staff or healthcare professional at each site. Any dose change must be recorded in the Dose Administration Record eCRF. The drug ampoule(s) must be retained for later evaluation by the monitor.

Screening

On Visit 1, no pasireotide LAR will be given to the patient.

Main Phase Treatment

The first pasireotide LAR 60 mg IM dose will be administered on Visit 2, after all baseline evaluations are completed and the eligibility to participate in the study is confirmed. Pasireotide LAR will be administered as a depot intragluteal IM injection.

Pasireotide LAR 60 mg IM will be administered by the site staff every 28 (± 3) days throughout the Main Phase treatment period (all patients are expected to receive 6 doses of pasireotide LAR every 4 weeks). A dose decrease to 40 mg will be allowed for safety reasons.

End of Study (EOS) Visit

After the Main Phase of the study (first 24 weeks of treatment), patients benefiting from pasireotide LAR treatment will be offered the opportunity to continue to receive pasireotide LAR, based on the physician's evaluation and the patient's wishes.

Patients who participate in the Extension Phase will be treated with pasireotide LAR for up to 92 weeks or approximately 2 years (Table 7-2), or until pasireotide or other effective therapy becomes commercially available, or until clinical benefit is no longer seen (whichever occurs first).

Extension Phase

Patients enrolled in the Extension Phase will receive pasireotide LAR IM at Visit 10 and will have the first extension study visit scheduled, which will occur 28 (± 3) days after Visit 10. Treatment with pasireotide LAR will be administered by the site's healthcare professional staff every 28 (± 3) days, during the Extension Period (see Table 7-2).

Additional Information on the Extension Phase:

The dose will continue to be 60 mg. If a patient is receiving 40 mg due to tolerability issues and such issues are resolved, there may be a dose escalation to 60 mg, at the physician's discretion. If the adverse event reoccur, the dose will be decreased to 40 mg and will be mantained until completion of the Extension Phase or until study discontinuation.

Safety Follow-up

All patients in the main and extension phases will be followed for safety for approximately 56 (± 3) days after administration of their last dose of pasireotide LAR.

6.4.1 Follow-up for dose-limiting toxicities

Patients whose treatment is interrupted or permanently discontinued due to an AE or abnormal laboratory value must be followed up at least once a week for 4 weeks, and in 4-week intervals thereafter, until resolution or stabilization of the event, whichever occurs first. All patients will be followed up for AEs and serious adverse events (SAEs) for 8 weeks after administration of the last dose of pasireotide LAR (refer to Section 6.4.4 for information on the discontinuation of the study drug).

6.4.2 Allowed study drug adjustments

For patients who cannot tolerate the administration schedule specified in the protocol, dose adjustments are allowed so that the patient may continue to receive the study drug.

The study drug for this study will be pasireotide LAR 60 mg given every 28 ± 3 days for 6 months, during the main study period. In case of tolerability issues (see Table 6-2), the pasireotide LAR dose may be decreased to 40 mg in the next scheduled injection. However, patients unable to tolerate the minimum dose of 40 mg will be discontinued from the study.

All dose changes must be recorded in the Dose Administration Record eCRF.

During the Extension Phase, if a patient receives 40 mg due to tolerability issues and such issues are resolved, there may be a dose escalation to 60 mg, at the physician's discretion. If the adverse event reoccurs, the dose will be decreased to 40 mg and the patient will maintain this dose.

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

Adverse event	Action
CTC Grade ≤ 2 AEs	No drug adjustment
CTC Grade ≥ 3 AEs evaluated as related to the study drug	Decrease intramuscular pasireotide LAR dose to 40 mg. If the AE does not improve to grade ≤ 2 with the 40 mg dose, the patient will be withdrawn.

The guidance above must be used for all AEs, except for changes in blood glucose and QTc and for liver safety monitoring. Blood glucose changes must be followed as described on Section 7.5.2.1. Changes in QTc interval must be followed as described on Section 7.5.2.2. Refer to Section 7.5.2.3 for liver safety monitoring.

6.4.3 Other concurrent medication

The investigator must instruct patients to notify the study site about any new medication administered after starting the study drug. All medications (except the study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with the study drug must be mentioned in the Concurrent Medication / Significant non-drug therapy eCRF after the study drug is started. If possible, there may be no changes in any concurrent medication during the study until all EOS evaluations are completed.

The use of anticoagulant medication should be avoided.

6.4.4 Discontinuation of the study drug

Patients experiencing unacceptable toxicity (grade ≥ 3 AE, including grade ≥ 3 changes in laboratory values) that the investigator considers as directly ascribable to the study drugs must have their doses decreased (Section 6.4.2) or be withdrawn from the study.

- Patients who permanently discontinue the study drug between Visit 2 and Visit 9 (inclusive) must be scheduled for the End of (Main) Study Visit (Visit 10) 28 ± 3 days after administration of the last dose of the study medication, when all evaluations listed will be performed. The Safety Follow-up Visit (Visit 11) will be performed approximately 56 ± 3 days after administration of the last dose of study medication.
- Patients who permanently discontinue the study drug in the Extension Phase must be scheduled for the End of (Extension) Study Visit 28 ± 3 days after administration of the last dose of the study medication, when all evaluations listed will be performed. The safety follow-up visit for the extension phase will be performed approximately 56 ± 3 days after administration of the last dose of the study medicaiton.

Patients who discontinue the study drug must be considered as withdrawn from the study after the EOS / Safety Follow-up evaluations are performed or when it's evident that the patient will not return for the EOS evaluations.

6.4.5 Early patient discontinuation

6.4.5.1 End of treatment

Patients may withdraw voluntarily from the study or be withdrawn, at the investigator's discretion, at any time. They may be considered as discontinued if they declare their intention to discontinue, or if they do not return for visits, or if they are lost to follow-up for any other reason. Patients may be withdrawn from the study by the investigator for any of the following reasons:

- Acute or progressive vision loss confirmed by a new evaluation of the visual field
- Increased tumor volume defined as tumor volume growth (>20%) and confirmed in a second MRI performed approximately one month later
- Pregnancy
- Adverse event(s)
- Uncontrolled diabetes mellitus
- Clinically significant abnormal laboratory value(s)
- Clinically significant abnormal result(s) of test procedures
- Protocol violation
- Lost to follow-up
- Administrative problems
- Death
- Patients who experience:
- ALT or AST > 3 x ULN and Total Bilirubin ≥ 2 x ULN and ALP < 2 x ULN
- ALT or AST > 5 x ULN and ≤ 8 x persistent ULN for more than 2 weeks
- ALT or AST > 8 x ULN

  If any of the discontinuation criteria is met, the study medication must be immediately discontinued. Additionally, appropriate safety follow-up monitoring must be performed, as defined on Section 7.5.2.3. Resuming the study medication after the discontinuation criteria are met is not allowed.

6.4.5.2 Completion of the study evaluation

For patients considered as lost to follow-up (i.e., patients whose condition is not clear because they did not attend the study visits without declaring an intention to discontinue), the investigator must show "due diligence" by documenting the actions taken in the source-documents in order to contact the patient, such as, for example, dates of phone calls, registered letters, etc.

7 Visits and evaluations schedule

Tables 7-1 **and 7-2** show a list of all evaluations for the Main Phase and the Extension Phase, respectively, and indicate with an "X" the visits to be performed. All data obtained from these evaluations must be confirmed in the patient's source-documentation. The table indicates which data are entered in the database (DB) or remain only on the source-documents (SD). The evaluations producing data for registration in the database and that are recorded in the eCRFs are listed using the eCRF name.

Table 7-1 Visits and evaluations schedule for the Main Study

Visit number	1	2	3	4	V401[E] 48	5	6	7	8	9	10 EOS[3]	11 Follow-up Visit [16]
Days [1]	Day -28 to -1	Day 0	Day 20	Day 28	Day 48	Day 56	Day 76	Day 84	Day 112	Day 140	Day 168	Day 196
Treatment week		Inclusion	Week 3	Week 4	Week 7	Week 8	Week 11	Week 12	Week 16	Week 20	Week 24	Week 28
	Screening [2]	Baseline/ Injection 1	Safety Only	Injection 2	Safety Only	Injection 3	Safety Only	Injection 4	Injection 5	Injection 6	Injection 7# (if the patient participates in the Extension Phase)	Safety Follow-up
Informed Consent Form (SD)	X											
Demographics (DB)	X											
Disease diagnosis and extent (DB)	X											
Relevant medical history / current medical conditions (DB)	X											
Evaluation of inclusion/exclusion criteria (SD)	X											
Vital signs (DB)	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination (SD)	X	X	X	X	X	X	X	X	X	X	X	X
Height (DB)	X											
Weight (DB)	X	X	X	X	X	X	X	X	X	X	X	X
Evaluation of symptoms / Disease-related symptoms [4] (DB)	X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance status (DB)	X	X	X	X		X	X	X	X	X	X	X
ECG (DB) [14]	X	X	X	X		X	X	X	X	X	X	
Blood pregnancy test[5,6]	X							X			X	
Hematology (DB)	X			X		X		X	X	X	X	

Visit number	1	2	3	4	V401[E] 48	5	6	7	8	9	10 EOS[3]	11 Follow-up Visit [16]
Days [1]	Day -28 to -1	Day 0	Day 20	Day 28	Day 48	Day 56	Day 76	Day 84	Day 112	Day 140	Day 168	Day 196
Treatment week		Inclusion	Week 3	Week 4	Week 7	Week 8	Week 11	Week 12	Week 16	Week 20	Week 24	Week 28
	Screening [2]	Baseline/ Injection 1	Safety Only	Injection 2	Safety Only	Injection 3	Safety Only	Injection 4	Injection 5	Injection 6	Injection 7# (if the patient participates in the Extension Phase)	Safety Follow-up
Coagulation parameter PT (D)	X	X	X[14]	X[14]	X[14]	X[14]	X				X	
Coagulation parameter APTT (D)	X	X					X				X	
Urinalysis [6] (DB)	X			X		X		X	X	X	X	
Fasting blood glucose, insulin [6]	X			X		X		X	X	X	**X**	
HbA1c [6]	X							X			X	
Chemistry [6,8] (DB)	X			X		X		X	X	X	X	
LFTs (ALT, AST, total bilirubin, albumin, ALP, γ-GT) (D)	X	X	X[14]	X[14]	X[14]	X[14]	X				X	
HBs-Ag and anti-HCV (D)	X											
Vitamin B12, folic acid[6]	X										X	
Hormone evaluation [6,9] (DB)	X			X				X			X	
Alpha subunit evaluation [6]	X			X				X			X	
Visual field evaluation [10](DB)	X	X[10]		X		X		X	X	X	X	
Gallbladder ultrasound (DB) [15]	X										X	
Pituitary / Sella turcica MRI [15]	X			X				X			X	
Adverse events (DB)		X	X	X	X	X	X	X	X	X	X	

Visit number	1	2	3	4	V401[E] 48	5	6	7	8	9	10 EOS[3]	11 Follow-up Visit [16]
Days [1]	Day -28 to -1	Day 0	Day 20	Day 28	Day 48	Day 56	Day 76	Day 84	Day 112	Day 140	Day 168	Day 196
Treatment week		Inclusion	Week 3	Week 4	Week 7	Week 8	Week 11	Week 12	Week 16	Week 20	Week 24	Week 28
	Screening [2]	Baseline/ Injection 1	Safety Only	Injection 2	Safety Only	Injection 3	Safety Only	Injection 4	Injection 5	Injection 6	Injection 7# (if the patient participates in the Extension Phase)	Safety Follow-up
Pasireotide LAR administration (DB)		X		X		X		X	X	X	X #	
Previous / concurrent medication [11] (DB)	X	X	X	X	X	X	X	X	X	X	X	
Study completion [13] (DB)												x[13]

The pasireotide dose in this visit will be administered to selected patients, at the physician's discretion, if the patient is included in the Extension Phase, based on the response evaluated by the investigator to the benefit from the drug (Section 6.4).

1. A ± 3 day window will be allowed for scheduled visits and evaluations, unless otherwise indicated.
2. To be performed before administration of the study drug.
3. To be performed if the patient discontinues early or upon completion of the study.
4. Disease-related symptoms to be evaluated: headache, visual disorders, fatigue, decreased libido, erectile dysfunction (only for men), irregular or interrupted menstrual cycles (only for non-menopausal women). The investigator will also ask patients to classify symptoms according to a 5-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe). The remainder will be evaluated as absent or present.
5. A pregnancy blood test will be performed at the final follow-up visit, if a patient reports a delay in menstruation or according to the physician's opinion.
6. Blood and urine must be collected before administration of the study drug. Patients must be fasting for 12 hours.
7. Hematology and coagulation include: hemoglobin, hematocrit (HCT), WBC count with differential, RBC count with differential, and platelet count; PT and APTT.
8. Complete chemistry includes: total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, calcium, phosphorus, chloride, sodium, potassium, inorganic phosphorus, creatinine, urea, uric acid, CPK, LDH, alkaline phosphatase, γ-GT, total protein, albumin, SGOT, SGPT, total bilirubin. If the total bilirubin concentration increases over 2.0 times the upper limit of normal, it must be differentiated in direct and indirect bilirubin at visits.
9. Hormone evaluations (blood) — pituitary disease evaluations: testosterone (for men), estradiol (for women), prolactin, free T4, TSH, LH, FSH, GH, IGF-I, cortisol, ACTH.

10. Evaluation by Standard Automated Perimetry (SAP). The Humphrey Field Analyzer is recommended. The window to perform the SAP must not be more than 7 days before the scheduled visit. If the visual field evaluation at Screening is performed no more than 14 days before Visit 2, it may be considered as baseline data and there is no need to repeat it for Visit 2.
11. Previous and concurrent medications comprise any therapy, including chemotherapy, radiation therapy, and surgery, or medication previously received, or ongoing treatment.
12. All medications / therapies used to treat tumor or symptoms in this study, given to a patient in a ≤ 4 week period after administration of the last dose of the study treatment, must be recorded in the eCRF. All patients will be followed up for safety for 56 days after administration of the last dose of the study drug.
13. Safety follow-up must be performed 56 ± 3 days after the patient has received the last pasireotide LAR dose. For patients who continue in the extension study, this visit will not be performed after the end of the main study, but 56 ± 3 days after the patient has completed the extension study.
14. The ECG will be performed before administration of the drug. On Visit 3 (Day 20) and on Visit 6 (Day 76), the ECG will be performed regardless of drug administration.
~~15.~~ .
15. The window to perform gallbladder MRI and US [ultrasound] must not be more than 7 days prior to the scheduled visit.
16. If a patient is not assigned to the Extension Phase, the follow-up visit will be Visit 11.

Table 7-2 Visits and evaluations schedule for the Extension Study

Visit	10[1]	11	12	402	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28 EOS	29 Follow-up [9]
Week	24	28	32	35	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96	Last dose + 8 weeks
Day	168	196	224	244	252	280	308	336	364	392	420	448	476	504	532	560	588	616	644	672	700
Injection	7	8	9		10	11	12	13	14	15	16	17	18	19	20	21	22	23	24		
Adverse events (DB)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Current medical conditions (DB)	X				X			X			X			X			X			X	X
Vital signs (DB)	X				X			X			X			X			X			X	X
Physical examination (SD)	X				X			X			X			X			X			X	X
Weight (DB)	X				X			X			X			X			X			X	X
Pituitary / Sella turcica MRI	X							X						X						X	
Alpha subunit [2]	X							X						X						X	
[redacted]																					
ECG (DB)	X				X			X			X			X			X			X	
Gallbladder ultrasound (DB)	X							X												X	
ECOG Performance status (DB)	X				X			X			X			X			X			X	X
Evaluation of symptoms / Disease-related symptoms (DB)	X				X			X			X			X			X			X	
Blood pregnancy test [2,10]	X							X						X						X	
Hematology (DB)	X							X						X						X	
Coagulation parameter PT (D)	XE	XK	XK	X	XK	XK				X	X	X	X	X	X	X	X	X	X	X	X
Coagulation parameter APTT (D)	XE					X				X	X	X	X	X	X	X	X	X	X	X	
Urinalysis [2] (DB)	X							X						X						X	
Fasting blood glucose and insulin [2]	X							X						X						X	
HbA1c [2]	X							X						X						X	
Chemistry [2,4]	X							X						X						X	
LFTs (ALT, AST, total bilirubin, albumin, ALP, γ-GT) (D)	X			X				X						X						X	

Visit	10[1]	11	12	402	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28 EOS	29 Follow-up [9]
Week	24	28	32	35	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96	Last dose + 8 weeks
Day	168	196	224	244	252	280	308	336	364	392	420	448	476	504	532	560	588	616	644	672	700
Injection	7	8	9		10	11	12	13	14	15	16	17	18	19	20	21	22	23	24		
Hormone evaluation [2,5] (DB)	X							X						X						X	
Evaluation of the visual field [6]	X							X						X						X	
Vitamin B12, folic acid [2]	X							X												X	
Administration of Pasireotide LAR [7] (DB)	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Previous / concurrent medication[8] (DB)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Completion of the study [9] (DB)																					X

[1] Patients who, according to the opinion of the physician in charge, are deriving benefit from pasireotide LAR treatment will be invited to participate in the extension phase.
[2] Blood and urine must be collected before administration of the study drug. Patients must be fasting for 12 hours.
[3] Hematology and coagulation include: hemoglobin, hematocrit (HCT), WBC count with differential, RBC count with differential, platelet count, PT, and APTT.
[4] Complete chemistry includes: total bilirubin, total cholesterol, LDL, HDL, triglycerides, creatinine, urea, uric acid, γ-GT, total protein, albumin, SGOT, SGPT, CPK, LDH, alkaline phosphatase, sodium, potassium, inorganic phosphorus, chloride, and calcium. If total bilirubin concentration increases over 2.0 times the upper limit of normal, total bilirubin must be differentiated in direct and indirect reagent bilirubin.
[5] Hormone evaluation (blood) — evaluations of pituitary disease: testosterone (for men), estradiol (for women), prolactin, free T4, TSH, LH, FSH, GH, IGF-I, cortisol, ACTH.
[6] Evaluation by Standard Automated Perimetry (SAP). The use of the Humphrey Field Analyzer is recommended. The window to perform the SAP must not exceed 7 days before the scheduled visit.
[7] Patients will continue to receive pasireotide LAR IM every 28 (± 3) days. Administration of the drug will be performed by a healthcare professional at the site. Administration of the last dose occurs on Week 92 (Visit 27).
[8] All medications / therapies used to treat the tumor and symptoms in this study, administered to a patient for 4 weeks or less after administration of the last dose of the study treatment, must be recorded in the eCRF. All patients will be followed up for safety for 56 ± 3 days after administration of the last dose of the study medication.
[9] The safety follow-up visit (Visit 29) must be performed 56 ± 3 days after the patient has received the last dose of pasireotide LAR.
[10] A blood pregnancy test will be performed at the final follow-up visit, if a patient reports delayed menstruation or according to the physician's opinion.

7.1 Information to be collected in case of screening failure

Patients who do not meet eligibility requirements on Visit 1 are considered as screening failures. If a patient cannot start treatment for any reason, this reason must be entered in the Screening Record eCRF, and the patient's demographics will be entered in the Demographics eCRF.

7.2 Demographics / other baseline patient characteristics

Patients' demographics and baseline characteristics will include the following: demographics, diagnosis and disease extent, relevant medical history / current medical conditions, previous / concurrent medication administered, physical examination, including vital signs, laboratory evaluations (including, but not limited to, fasting blood glucose and insulin), urinalysis, visual field and radiological evaluations, alpha subunit level, and [redacted], if applicable.

Evaluations performed to determine eligibility include gallbladder imaging, MRI, ECG, ECOG performance status, and pregnancy blood test. Other safety tests include AEs and SAEs, hematology and coagulation, and chemistry evaluations.

The data will be recorded in the applicable eCRFs.

7.3 Treatments

The study medication administered during the study must be documented in the Dose Administration eCRF. Date and time of dose administration will be recorded in the Dose Administration Record. Compliance will be evaluated by the investigator and/or study staff on all visits. Records of study drug used, treatment administered, and intervals between visits will be kept throughout the study. Drug accountability will be registered by the field monitor during site visits and upon completion of the study.

All drugs, including over-the-counter drugs and previous therapies for the disease, taken before administration of the study drug and continuing throughout this study must be documented in the Previous / Concurrent Medication eCRF.

In the Main Phase, patients will receive the study drug on Visit 2 (Day 0) and then every 4 weeks (28 ± 3 days) thereafter, i.e., on Weeks 4, 8, 12, 16, 20. Patients who enter the Extension Phase will receive the study drug starting on Week 24, and then every 4 weeks (28 ± 3 days) thereafter, until Week 92.

All therapies administered to a patient within 4 weeks after administration of the last dose of the study medication must be documented in the Therapy Since Discontinuation eCRF.

7.4 Efficacy

Tumor volume, hormone response, and relevant disease-related symptoms will be evaluated, as previously described in this protocol.

7.4.1 Primary efficacy evaluation

Tumor volume will be evaluated by MRI with gadolinium contrast in the Screening Phase (and will be considered as baseline imaging), on Weeks 4, 12, and 24 in the Main Phase, and on Weeks 48, 72, and 96 in the Extension Phase (see Tables 7-1 and 7-2).

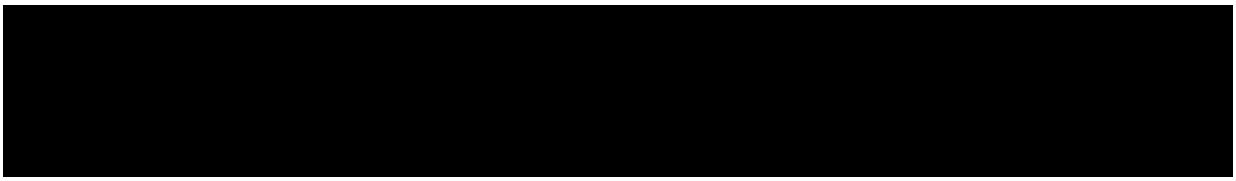
7.4.2 Secondary efficacy evaluations

Tumor volume will also be evaluated as described on Section 7.4.1. Time to response will also be obtained (i.e., time to reach tumor volume decrease ≥ 20%).

Disease-related symptoms will be reported by patients and recorded by the medical staff, on all Main Phase visits and on visits 13 (week 36), 16 (week 48), 19 (week 60), 22 (week 72), 25 (week 84), and 28 (week 96) of the Extension Phase.
Disease-related symptoms to be evaluated: headache, visual disorders, fatigue, decreased libido. Only for men: erectile dysfunction. Only for non-menopausal women: irregular or interrupted menstrual cycles. The investigator will also ask patients to classify the symptoms above according to a 5-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe). The remaider will be evaluated as absent or present.

Hormone profiles, including growth hormone (GH), insulin-like growth factor I (IGF-1), follicle-stimulating hormone (FSH), luteinizing hormone (LH), adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), prolactin (PRL), cortisol, free T4, and estradiol (for women) or testosterone (for men), will be evaluated in the Screening Period (and will be considered as baseline data) and on Weeks 4, 12, and 24 of the Main Phase. Evaluations in the Extension Phase will be performed on Weeks 48, 72, and 96.

Alpha subunit levels will be measured in the Screening Period (and will be considered as baseline data), on Weeks 4, 12, and 24 in the Main Phase, and on Weeks 48, 72, and 96 in the Extension Phase.



7.5 Safety

7.5.1 Adverse events

An AE for the purposes of this protocol is the onset of (or worsening of) untoward (pre-existing) sign(s), symptom(s), or clinical condition(s) occurring after signature of the Informed Consent Form, even if the event is clearly considered not related to the study drug(s). Refer to Section 6 for specific protocol definitions of study drug and study treatment.

AEs will be evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. If there is no CTCAE classification for an adverse event, mild, moderate, severe, and potentially fatal severities **or** grades 1 to 4 will be used. CTCAE grade 5 (death) will not be used in this study; this information will be gathered in the End of Treatment or Survival Information eCRF. AE monitoring must continue for at least 4 weeks after administration of the last dose of the study treatment.

AEs occurring before the study treatment is started, and after the Informed Consent Form is signed, are recorded in the Medical History / Current Medical Conditions electronic Case Report Form.

Abnormal laboratory values or abnormal test results only constitute AEs if they lead to clinical signs or symptoms, are considered clinically significant, or require therapy (e.g., any hematological abnormality requiring transfusion or treatment with cytokines), and must be recorded in the Adverse Events eCRF according to associated signs, symptoms, or diagnoses. Additionally, single abnormal laboratory values that are considered clinically significant (for example, causing study discontinuation or constituting, themselves, a serious adverse event) must be recorded in the Adverse Events eCRF. SAEs occurring after the Informed Consent Form is signed are recorded in the Adverse Event eCRF.

The occurrence of AEs must be obtained by means of indirect questioning to the patient on every visit throughout the study. AEs may also be detected when voluntarily reported by the patient during or between visits or through physical examination, laboratory tests, or other evaluations. Whenever possible, each AE must be evaluated to determine:

1. Severity grade (CTCAE grade 1 - 4)
2. Relationship to pasireotide LAR (suspected / non-suspected)
3. Duration (onset and end dates or if ongoing at the final examination)
4. Action taken (no action taken; study drug dose adjusted / temporarily interrupted; study drug permanently discontinued due to this AE; concurrent medication administered; non-drug therapy administered; hospitalization / prolonged hospitalization)
5. If serious, a serious adverse event (SAE) is defined as an event that:

- Is fatal or potentially fatal
- Results in persistent or significant disability / incapacity
- Constitutes a congenital anomaly / birth defect
- Requires hospitalization or prolongation of ongoing hospitalization, unless the hospitalization is for:
  - Routine treatment or monitoring of the indication studied; not associated to any condition deterioration (specify what this includes)
  - Elective or pre-planned treatment to a pre-existing condition that is not related to the study indication and did not worsen since the consent form was signed
  - Emergency outpatient treatment for an event that does not meet any of the SAE definitions provided above and does not result in hospitalization
  - Social reasons and temporary care in the absence of any deterioration of the general patient condition
- Is clinically significant, i.e., defined as an event that puts the patient at risk or that might require medical or surgical intervention to prevent one of the results listed above

Unlike routine safety evaluations, SAEs are continuously monitored and have special reporting requirements; See Section 8.1.

All AEs must be properly treated. This treatment may include changes in treatment with the study drug, including possible interruption or discontinuation, start or interruption of concurrent treatments, changes in the frequency or nature of evaluations, hospitalization, or any other clinically required intervention. Once an AE is detected, it must be followed up until its resolution, and an evaluation must be performed on every visit (or more frequently, if required) regarding any change in severity, its suspected relationship to the study drug(s), any interventions required to treat it, and its outcome.

The information on already known common side effects related to the investigational drug may be found in the Investigator's Brochure (IB) or will be notified between IB updates as Investigator Notifications (INs). This information will be included in the patient's informed consent form and must be discussed with the patient during the study, as required.

7.5.2 Special Safety

7.5.2.1 Changes in blood glucose

The principal investigator must instruct patients about signs and symptoms of hyperglycemia, and evaluate the risks of hyperglycemia in all patients. It is recommended to follow the guidelines established by international associations specialized in diabetes, such as the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) (Nathan 2009).

Patients with history or recent diagnosis of fasting glucose impairment, glucose tolerability impairment, diabetes mellitus, or at risk of developing these conditions must monitor blood glucose by means of a fingerstick capillary glucose test twice a day (fasting and 2 hours post-prandial). It is recommended that patients be encouraged to keep a blood glucose diary for appropriate disease management throughout the study, as well as to show the data collected to the physician / diabetes expert for evaluation. The data will not be collected by the sponsor.

It is advised that any patient experiencing fasting plasma glucose > 130 mg/dL (7.2 mmol/L), or 2-hour post-prandial capillary glucose (PPG) ≥ 180 mg/dL (10 mmol/L) in two consecutive measurements with an interval of approximately 14 days and/or HbA1c > 7% be evaluated by an diabetes expert for proper treatment (Position statement ADA 2010). Additionally, these patients must be informed on diabetes control. The start or adjustment of anti-hyperglycemic treatment must be considered as soon as possible, at the discretion of the diabetes expert. Additionally, these patients must start blood glucose monitoring by fingerstick capillary glucose test twice a day (fasting and 2 hour post-prandial) if it has not yet been performed. It is recommended that patients be encouraged to keep a blood glucose diary for appropriate disease management throughout the study, as well as to show the data collected to the physician / diabetes expert for evaluation. The data will not be collected by the sponsor.
Patients developing symptoms of uncontrolled diabetes mellitus and/or blood glucose levels consistently above 275 mg/dL (15.5 mmol/L), in spite of appropriate therapeutic interventions, must be discontinued from the study, as well as those patients whose HbA1c percentage is ≥ 10%, in spite of appropriate therapeutic interventions.

7.5.2.2 Changes in QT interval

If, at any visit, a QTcF > 480 msec is seen in patients receiving pasireotide LAR, the following actions will be taken:

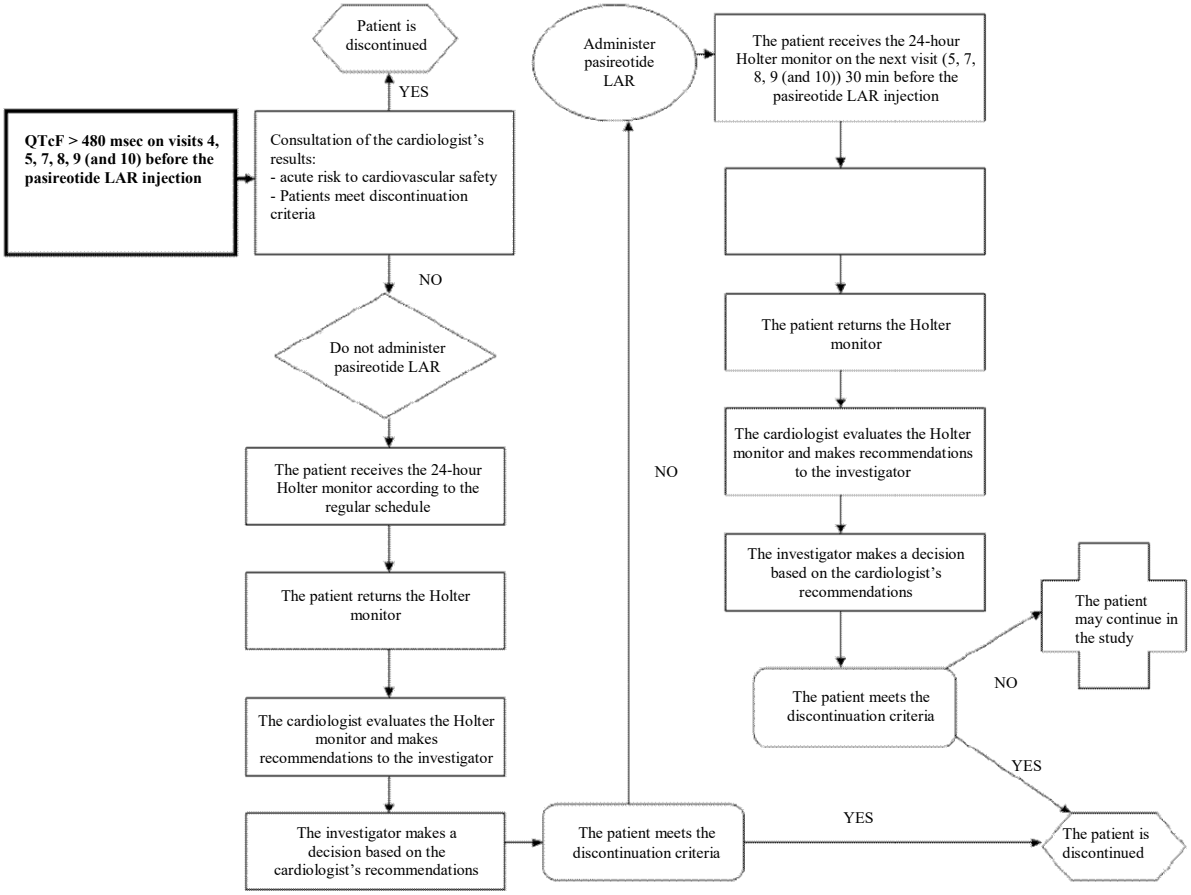
- A visit to a cardiologist must be scheduled as soon as possible, but within no more than 7 days of the initial abnormal ECG, and the cardiologist must re-evaluate the ECG (this can be done by the central cardiologist, if the study has one).
  - If a QTcF > 480 msec is NOT confirmed, no action will be taken.
  - If a QTcF > 480 msec is confirmed, a cardiologist must perform a thorough examination (such as review of baseline ECG, concurrent medication, and performance of a cardiovascular examination (including, at least, one cardiac auscultation)) in order to evaluate the patient for cardiovascular risk factors.
  - If, based on the cardiologist's evaluation, the investigator considers that there is an acute cardiovascular safety risk and that the patient should not continue to receive the study drug, or the patient meets any discontinuation criteria (section 6.4.5.1), he/she must be immediately discontinued.

- If, after the cardiologist's examination, the investigator considers that there is no acute cardiovascular safety risk and that the patient may continue to receive the study drug, then, the following actions must be taken:

- Scenario A (Figure 7-1): If the initial ECG was performed before the pasireotide LAR injection:
  A (24-hour) Holter ECG must be recorded as soon as possible, but within no more than 7 days of the initial abnormal ECG. The cardiologist evaluates the Holter ECG and provides the investigator with recommendations. The investigator analyzes the results and the cardiologist's recommendations. If a patient meets the discontinuation criteria (**section 6.4.5.1**), he/she will be immediately discontinued.
  If a patient does not meet the discontinuation criteria, the next pasireotide LAR dose may be administered. A second Holter ECG must be recorded on the day of the next pasireotide LAR injection, and it must be started 30 min before the study drug injection. ECG, cardiac examination, and Holter ECG results, as well as the cardiologist's recommendation, must be evaluated by the investigator in order to determine whether the patient may or may not continue in the study (discontinuation criteria to be followed, Section 6.4.4 and Section 6.4.5).
  If an abnormal ECG is seen on Visit 10 and no additional dose of pasireotide LAR is administered, then the follow-up is at the investigator's discretion.

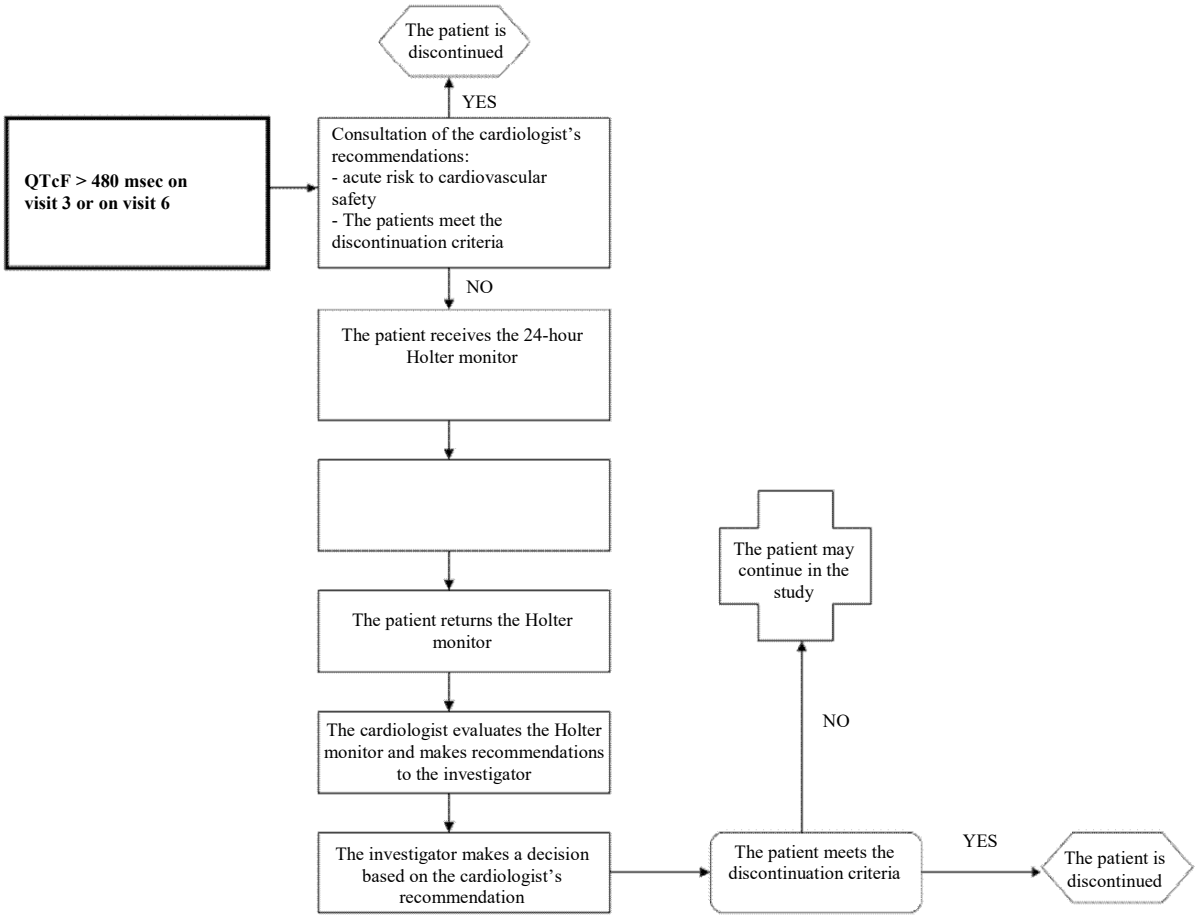
- Scenario B (Figure 7-2): If the initial ECG is performed at Visit 3 (Day 20) or at Visit 6 (Day 76):
  A (24-hour) Holter ECG must be recorded as soon as possible, but within 7 days of the initial abnormal ECG. The cardiologist evaluates the Holter ECG and provides the investigator with recommendations. The investigator analyzes the results and the cardiologist's recommendations. If a patient meets the discontinuation criteria (Section 6.4.4 and Section 6.4.5), he/she will be immediately discontinued. If the investigator decides that the patient may continue in the study, he/she will be invited to return to the next regular visit, according to the visits and evaluations schedule (Table 7-1).

Figure 7-1 Scenario A: Procedure for QTcF Prolongations Occurring on the Planned Pasireotide LAR Dosing Visits



Visit 10: If QTcF > 480 msec on this visit and no additional pasireotide LAR dose is administered, then the follow-up is at the investigator's discretion.

Figure 7-2 Scenario B: Procedure for QTcF Prolongations Occurring on visits 3 and 6 Planned Only for Patients Receiving Pasireotide LAR



7.5.2.3 Liver safety monitoring

If any of the criteria below is observed on any scheduled or unscheduled visit, the sponsor must be informed as soon as the occurrence is acknowledged.

- ALT or AST > 3 x ULN and Total Bilirubin ≥ 2 x ULN
- ALT or AST > 5 x ULN and ≤ 8 x ULN
- ALT or AST > 8 x ULN

The following tests will be performed immediately within **72 hours** after the abnormality is acknowledged:

- Perform liver-oriented medical history and physical examination (i.e., evaluate occupational risks, concurrent medication, including over-the-counter medication, concurrent disease, etc.)

- Liver tests: ALT, AST, total bilirubin (bilirubin fractionated in direct / indirect, if total bilirubin is > 2.0 x ULN), Albumin, PT (INR), ALP, and γ-GT
- Perform hepatitis tests: anti-HAV IgM (to confirm acute Hepatitis A), HBsAg, anti-HBc, anti-HCV (if positive, viral load PCR must be evaluated), anti-HEV, ANA antibodies, anti-smooth muscle antibodies, CMV and EBV
- Perform abdominal ultrasound (liver and bile duct)
- Collect pharmacokinetic samples and record the level and time of the last dose the patient received before the pharmacokinetic sample.

Liver function tests must be monitored every **3 - 4 days** until resolution or return to baseline level.

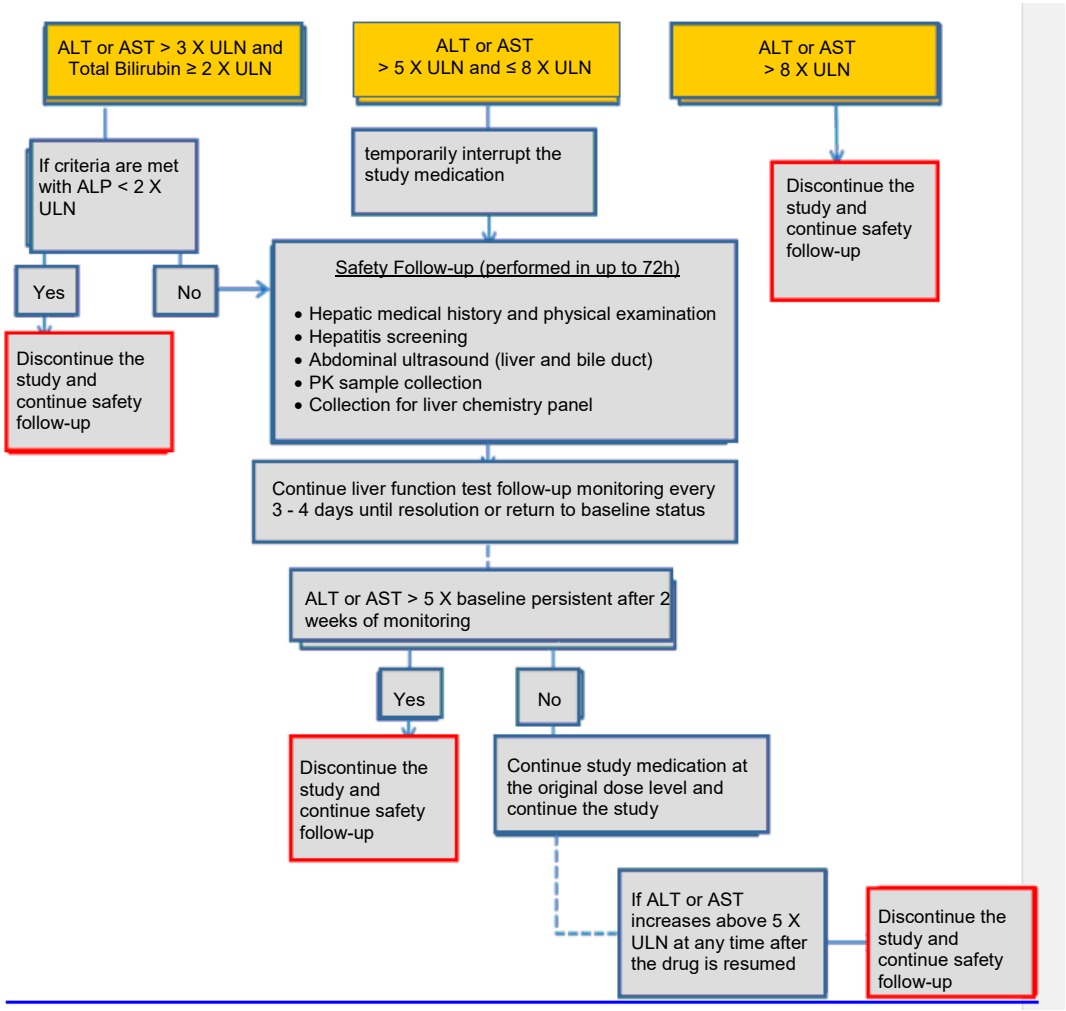
Patients may need to be discontinued if the abnormal liver function criteria are met when the liver tests are repeated (refer to discontinuation criteria on Section 6.6.5.1). The reports of the course of the event must be kept until resolution or stabilization (i.e., no elevation after 2 consecutive evaluations).

For ALT or AST > 5 x ULN and ≤ 8 x ULN, the following must occur (in addition to the safety follow-up procedures listed above):

- The study medication must be temporarily interrupted and the liver tests monitored every **3 - 4 days** until resolution or return to baseline level.
- If no resolution or return to baseline occurs after 2 weeks, the patient must be discontinued.
- If ALT or AST return to less than 5 x ULN, the study medication may be resumed and the patient may continue the study according to the protocol.
- If ALT or AST increase to over 5 x ULN at any time after the study medication is resumed, then the study medication must be immediately discontinued.

If any of these criteria is met and considered as an adverse event by the investigator, the event must be recorded on the Adverse Event page of the case report form; if the event is considered severe by the investigator, then proceed to complete the SAE form. Additionally, any significant finding of the physical examination must be recorded in the Adverse Event page of the case report form.

Figure 7-3 Liver Test Monitoring Algorithm



7.5.2.4 Gadolinium

There are known adverse events after the use of Gadolinium as contrast material in MRI scans. Caution must be taken with patients with current and previous renal failure.

7.5.3 Physical examination, weight, height

Physical examinations will be performed and weight will be measured on all visits. This may be performed by the Investigator or any other qualified healthcare professional. The information on physical examinations must be present in the source-documentation at the study site. Height will be registered only during the screening / baseline period. Significant

findings present before the start of the study treatment must be included in the Relevant Medical History / Current Medical Conditions Case Report Form. Significant findings after the start of the study drug meeting the definition of an AE must be recorded in the Adverse Event Case Report Form (eCRF).

7.5.4 Vital signs

Body temperature, blood pressure in supine position, and heart rate in supine position will be evaluated on all main phase visits and on Visits 13 (week 36), 16 (week 48), 19 (week 60), 22 (week 72), 25 (week 84), 28 (week 96), and 29 (week 100) in the extension phase.

7.5.5 Performance status

Eastern Cooperative Oncology Group (ECOG) performance status will be evaluated on each visit in the main phases and on Visits 13 (week 36), 16 (week 48), 19 (week 60), 22 (week 72), 25 (week 84), 28 (week 96), and 29 (week 100) in the extension phase, using the criteria on Table 7-3.

Table 7-3 Eastern Cooperative Oncology Group (ECOG) performance status scale

Grade	ECOG
0	Fully active, able to carry out all pre-disease activities without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and awake for approximately more than 50% of time.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Unable to carry out any self-care. Completely confined to bed or chair.
5	Deceased

7.5.6 Laboratory evaluations

Laboratory samples will be submitted to a local laboratory for analysis, except alpha subunit [redacted], which will be submitted to a central laboratory. Patients will fast overnight for 12 hours before all blood samples are collected. Blood samples must be performed in the morning. Drinking water is allowed during this period.

Details about the central laboratory, including collection and submission of samples, report of results, and warning procedures for extreme values, will be provided in the Investigator's Binder.

7.5.6.1 Hematology

Hematology parameters will be evaluated in the Screening Period, before administration of the study drug, and on every Main Phase visit (except Visit 2, Visit 3 [Week 3], Visit 6 [Week 11], and Visit 10 [Week 24]), and will include: WBC count with differential, hemoglobin, HCT, RBC count and platelet count, and differential.

7.5.6.2 Coagulation

Coagulation parameters APTT and PT will be evaluated on visit 1 (screening), visit 2 (baseline), visit 6, and visit 10 (completion of the study) for all patients. Coagulation parameter PT will also be evaluated on visit 3, visit 4, visit 401 (after 48 days), and visit 5 for patients randomized to the double-blind treatment arm of pasireotide LAR. Coagulation parameters will be collected before administration of the study drug.

During the Extension Phase, evaluations will be performed first on visit 10 (Week 24), and then every 6 months thereafter (i.e., Weeks 48, 72, and 96).

7.5.6.3 Chemistry

A complete chemistry profile will be evaluated in the screening period and before administration of the study drug on each visit (except on Visit 2, Visit 3, Visit 6, and Visit 11, the Follow-up Visit) and will include: total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, calcium, phosphorus, chloride, sodium, potassium, inorganic phosphorus, creatinine, urea, uric acid, CPK, LDH, alkaline phosphatase, γ-GT, total protein, albumin, SGOT, SGPT, total bilirubin. In the Extension Phase, the chemistry profiles will be evaluated on visit 10 (Week 24) and then every 6 months thereafter (Weeks 48, 72, and 96).

If total bilirubin concentration increases more than 2.0 times the upper limit of normal, total bilirubin must be differentiated in direct and indirect reagent bilirubin on all visits.

Fasting blood glucose, insulin, and fasting chemistry evaluations will be performed in the screening phase and before administration of the study drug on each visit, except on Visit 2, Visit 3 (Week 3), Visit 6 (Week 11), and Visit 11 (Week 28, Follow-up Visit) in the Main Phase; they will also be performed on Weeks 48, 72, and 96 in the Extension Phase.

Liver function tests (ALT, AST, total bilirubin, albumin, ALP, and γ-GT) will be evaluated on visit 1 (screening), visit 2 (baseline), visit 6, and visit 10 for all patients. Liver function tests will also be evaluated on visit 3, visit 4, visit 401 (after 48 days), and visit 5.

HbA1c evaluations will be performed in the screening period (these will be considered as baseline data), on Weeks 12 and 24 in the Main Phase, and on weeks 48, 72, and 96 in the Extension Phase.

Vitamin B12 and folic acid evaluations will be performed in the Screening Period (these will be considered as baseline data), on Week 24 in the Main Phase, and on weeks 48 and 96 in the Extension Phase.

7.5.6.5 Serology

Hepatitis B surface antigen (HBs-Ag) and Hepatitis C antibody (anti-HCV) tests will be performed on visit 1 (screening).

7.5.6.6 Urinalysis

Specific gravity, pH, glucose, protein, bilirubin, ketones, leukocytes, and blood will be evaluated. Urine must be collected in the Screening Phase and before administration of the study drug on each visit (except on Visit 2, Visit 3, Visit 6, and Visit 11 or Follow-up Visit) in the Main Phase and on Weeks 48, 72, and 96 in the Extension Phase.

7.5.6.7 Pregnancy test

Blood pregnancy test is performed in the screening period, on Weeks 12 and 24 in the Main Phase, and on Weeks 48, 72, and 96 in the Extension Phase. It may be performed on the Follow-up Visit (56 ± 3 days after the last dose of the study medication) if the patient reports late menstruation or at the physician's discretion. Patients considered post-menopausal (defined as 12 months of natural (spontaneous) amenorrhea **or** 6 months of spontaneous amenorrhea with FSH blood levels > 40 mIU/mL before or during the study) are not required to performed subsequent pregnancy tests.

The study drug treatment must be withdrawn in case of pregnancy.

In order to ensure patient safety, every pregnancy in a patient under study drug administration must be reported to Novartis within 24 hours after acknowledgement. Pregnancy must be followed to determine the outcome, including miscarriage or abortion, details about the birth and presence or absence of any birth defects, congenital anomalies or maternal and/or newborn complications.

For information on pregnancy reports, refer to section 8.2.

7.5.7 Radiology tests

A **gallbladder ultrasound** will be locally performed in the Screening Phase (this will be considered as baseline data), on Week 24 in the Main Phase, and Weeks 48 and 96 in the Extension Phase. Patients with history of symptomatic colelithiasis are excluded from participation in the study (refer to Section 5.2). Information on the presence and location of gallstones, gallbladder sediments, and bile dilation will be entered in the Gallbladder Ultrasound eCRF page. In case of abnormal liver function criteria (refer to Section 7.5.2.3), an abdominal ultrasound will be required (liver and bile duct).

MRI Evaluation / Tumor volume measurement:

Patients will undergo MRI evaluations in the Screening Phase (these will be considered as baseline data), and on Visits 4 (Week 4), 7 (Week 12), and 10 (Week 24). MRIs will be evaluated by a central reviewer. At least 4 MRIs are expected to be evaluated by central review during the Main Phase of the study. In the Extension Phase, MRI evaluations will be performed on Weeks 48, 72, and 96.

Coronal and sagittal images weighted at T1 will be obtained before and after administration of gadolinium contrast. The minimum scanner field power will be 1.5 T.

MRIs will be submitted for evaluation by a blinded central evaluator. In order to ensure consistency in all participating sites, MRIs must be performed and processed according to the guidelines of the central evaluator's facility, which will be distributed to the sites before study start. These pituitary adenomas will be measured for analysis by a neuro-radiologist, using manual tracing together with the imaging analysis software.

Total tumor volume will be derived from coronal image with gadolinium and estimated by multiplying each slice thickness by the area within the curve of the imaging with manual tracings and adding the slices' volumes. The largest diameter at any plan will determine the maximum diameter of the tumor.

A change $\geq 20\%$ in the original volume of the tumor will be considered clinically significant. Smaller changes in pituitary tumor volumes may be attributed to volume measurement artifacts, changes in the position of the slice, or time of administration of the contrast bolus (Jimenez et al 2008)(Colao et al 2009).

7.5.8 Electrocardiogram (ECG)

All ECGs will be locally performed. An ECG will be performed in the Screening Period or Visit 1 (to evaluate eligibility) and then on all visits before injection of the study drug in the Main Phase, except for Visits 3 and 6, on which they will be performed independently of drug administration. In the Extension Phase, ECGs will be performed on Weeks 36, 48, 60, 72, 84, and 96.

It is recommended that paper speed be programmed to 25 mm/s, and sensitivity to 10 mm/mV (calibration). The operator must sign and date all tracings performed. The abnormalities seen must be recorded in the ECG eCRF.

If a clinically significant abnormality is detected, the ECG will be repeated, at the Investigator's discretion, until the abnormality is resolved. More frequent ECGs may be performed at the Investigator's discretion, if clinically indicated. Any abnormalities must be recorded in the unscheduled evaluation pages of the eCRF.

Data safety records must include the following:
• Any abnormal ECG findings (refer to Section 7.5.2.2)
• Abnormal vital signs
• All arrhythmias, including: Torsades de Pointes, ventricular tachycardia, ventricular fibrillation, and ventricular flutter
• Syncope, near-syncope, and fainting
• Seizures or loss of central function (sudden incontinence, dizziness, visual disorders)
• Sudden death

The study number must be recorded as [CSOM230D2401] at each tracing and must be kept in the source-documents.

7.5.9 Visual evaluations

Visual field evaluations will be performed at screening, on Visit 2 (if the visual field evaluation at Screening is performed no more than 14 days before Visit 2, it may be considered as baseline data and there is no need to repeat it for Visit 2), on all visits in the Main Phase, except for Visit 3 and 6, and on Weeks 48, 72, and 96 in the Extension Phase.
The window to perform the visual field evaluation must be of no more than 7 days before the scheduled visit.

Standard Automated Perimetry (SAP) is the most frequently used parameter to estimate the severity of visual loss (Monteiro et al 2009). The use of a Humphrey Field Analyzer is recommended.

Visual Field Test

The visual field test will be performed using SAP. The use of a Humphrey Field Analyzer is recommended. The perimeter software will use the refractive correction for near vision, calculated according to the patient's age (Monteiro et al 2009).

These test reports will determine whether the visual field is **normal or abnormal**. If abnormal, it will be classified as:

- **mild** (corrected visual acuity within normal limits (better than 20/30), in addition to nasal visual field within normal limits and impairment of approximately one quadrant of the temporal visual field) or
- **severe** (impaired corrected visual acuity (20/30 or worse), or impaired nasal visual field or impairment of more than one quadrant in the temporal visual field).

Outcome information will also be provided in the follow-up report: **Stable, improved, or worsened** visual field.

7.6 Tolerability

In addition to overall safety data, information on dose decreases will be collected. Furthermore, any AEs related to the study drug, e.g., gastrointestinal disorders, glucose metabolic disorders, cardiac dysfunctions, laboratory abnormalities, infections, and injection site reactions, will be summarized through the submission of counts and percentages for each treatment group.

7.7 Patient reported outcomes

Not applicable.

8 Safety monitoring

8.1 Serious adverse event reporting

In order to ensure patient safety, each SAE, **regardless of the suspected causality**, occurring after the beginning of any period in which the study protocol interferes with the standard medical care given to the patient (for example, withdrawal of treatment during washout period, change in treatment for a fixed dose of concurrent drug) and up to 56 days after the patient receives the last IM LAR injection of the study drug must be reported to Novartis within 24 hours after acknowledgement. Any SAE experienced after this period must be reported to Novartis if the investigator suspects that there is a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as a follow-up to the original episode within 24 hours of receipt of the follow-up information by the investigator. A SAE occurring in a different timepoint or considered as not otherwise related to a previously reported event, must be reported separately as a new event.

The information about all SAEs is collected and recorded in the Serious Adverse Event Report Form. The investigator must evaluate and register the relationship between each SAE and each specific study drug (if there is more than one study drug), complete the SAE Report Form in English, and fax it, completed and signed, within 24 hours to the Novartis Integrated Medical Safety (IMS) Oncology Department.

The site-specific phone and fax numbers of the contact people at the local IMS department are indicated in the investigator's binder provided to each site. The original copy of the SAE Report Form and the fax confirmation page must be kept together with the documentation of the case report form at the study site.

Follow-up information is submitted to the same person as the original SAE Report Form, using a new SAE Report Form, indicating that this is a follow-up of a previously reported SAE and mentioning the date of the original report. Each recurrence, complication, or progression of the original event must be reported as a follow-up to that event, regardless of when it occurs. Follow-up information must describe whether the event resolved or continues, whether and how it was treated, whether there was unblinding or not, and whether the patient continued or discontinued his/her participation in the study.

If the SAE is not previously documented in the Investigator's Brochure or the Package Insert (new occurrence), and if it is considered related to the Novartis study drug, an associate from Novartis IMS Oncology Department may request emergency additional information to the investigator for notification of the Health Authority. Novartis may need to issue an IN to inform all investigators involved in any study with the same medication reported for this SAE. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to relevant authorities and ethics committees, according to Directive 2001/20/EC or according to the national regulatory requirements in the participating countries.

8.2 Pregnancy

In order to ensure patient safety, every pregnancy in a patient under administration of the study drug must be reported to Novartis within 24 hours from acknowledgement of its occurrence. Pregnancy must be followed up in order to determine the outcome, including miscarriage or abortion, details about the birth, and presence or absence of any birth defect, congenital anomalies, or maternal and/or newborn complications.

Pregnancy must be recorded in a Clinical Trial Pregnancy Form and reported by the investigator to the Local Novartis Integrated Medical Safety (IMS) Department. The pregnancy follow-up must be recorded in the same form and must include an evaluation of the possible relationship of any pregnancy outcome to the Novartis study drug. Any SAE experienced during pregnancy must be reported in the SAE Report Form.

Information about pregnancy of female partners of any men receiving the study drug during the study must be collected. The consent to report the information about this pregnancy must be obtained from the mother.

9 Data review and management

9.1 Site monitoring

Before the study is started, in a site initiation visit or in a meeting with the investigator, the Novartis team (or an appointed CRO) will review the protocol and eCRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check for correct completion of patient records, accuracy of eCRFs records, compliance with the protocol and Good Clinical Practice (GCP), enrollment progress, and ensure that the study drug is stored, dispensed, and accounted for according to specifications. The main study staff must be available to assist the field monitor during these visits.

The investigator must keep the source-documents for each patient in the study, consisting of case and visit notes (hospital or clinic records) containing demographics and medical information, laboratory data, ECGs, and results of any other tests or evaluations. All information contained in the eCRFs must be traceable to these source-documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must facilitate the monitor's access to all relevant source-documents to confirm their consistency with the insertions in the eCRF. Novartis monitoring rules require complete verification for presence of the consent form, compliance with inclusion / exclusion criteria, documentation of SAEs, and recording of data that will be used for all primary and safety variables. Additional verifications regarding the consistency of the source-data with eCRFs are conducted according to the specific monitoring plan for the study. No information on the source-documents about the patients' identity will be disclosed.

9.2 Data collection (eCRF)

The investigator's designated staff must enter the information required by the protocol in the Novartis eCRFs. Field monitors will review the eCRFs for completion and accuracy and will instruct the site personnel to perform any corrections or inclusions required.

9.3 Database management and quality control

The data of eCRFs are entered in the study database by the CRO Data Management team after its own internal standard operating procedures are reviewed and approved by Novartis.

Then, the data entered are systematically verified by the CRO Data Management team with the use of error messages printed from validation programs and database listings. Obvious errors are corrected by the CRO Data Management personnel. Other errors or omissions are entered in electronically created Data Query Forms. The investigator (or his/her designee) will answer / resolve the query directly in the system. All changes are recorded in the study audit, which will capture who, when, and what files were corrected / changed. Quality control auditing of all main safety and efficacy data in the database is performed before database lock.

Concurrent medication entered in the database will be coded with the use of the WHO Drug Reference List, which uses the Anatomical Therapeutic Chemical (ATC) classification system. The medical history / current medical conditions and AEs will be coded with the use of the terminology of the Medical Dictionary for Regulatory Activities (MedDRA).

Laboratory samples, which will be centrally processed, will have their results submitted to the investigators.

ECG readings will be locally processed and the results will be entered in the eCRF.

The occurrence of any protocol breach will be determined. After the completion of these actions and after the database is declared complete and accurate, it will be locked and made available for data analysis. Any subsequent changes in the database may be performed only upon mutual written agreement between the Global Head of Biostatistics and Statistical Reporting and the Global Head of the Therapeutic Area.

10 Statistic methods and data analysis

The following sections describe the analyses to be performed.

For the Main Phase of the study, efficacy and safety analyses will be performed with the data collected when all patients enrolled complete their EOS visit. All Follow-up Visit safety data from patients who do not enter the Extension Study will also be included in the safety analyses of the Main Study. A final analysis will be performed when all Extension patients complete their last visit and will be reported either as an additional clinical study report or as an amendment to the Main Phase report. The other additional data at the end of the main study will be analyzed and summarized later in an additional clinical trial report or in a main study report.

Novartis or the designated CRO will analyze all data using the SAS System for data analysis V8.0 or higher. Any data analysis performed independently by an investigator must be submitted to Novartis before its publication or presentation.

Data from all participating sites in this study will be pooled so the appropriate number of patients is available for analysis. The statistical analysis methods described in this section will focus on the data analysis in the main study. Similar methods will be used in the analyses during the extension phase, as appropriate.

10.1 Analysis populations

Full analysis set (FAS): comprises all patients successfully completing Screening and receiving at least one dose of the study medication. The FAS will be the primary analysis set for efficacy analyses.

Safety analysis set: comprises all patients receiving at least one dose of the study drug and having at least one post-baseline safety evaluation.

It is noteworthy that the statement that a patient did not experience AEs (in the Adverse Event eCRF) constitutes a safety evaluation. The safety set will be used for all safety analyses.

The analyses presented in these sections correspond to the analyses to be used for the Main Phase of the study. A final analysis will be performed when all Extension patients complete their last visit and will be reported either as an additional clinical study report or as an amendment to the Main Phase report.

10.2 Demographics / other baseline patient characteristics

Demographics and other baseline data, including disease characteristics (e.g., age, gender, and race), will be descriptively summarized based on the FAS. Categorical data will be presented as frequencies and percentages. For continuous data, the mean, standard deviation, median, minimum, and maximum will be presented.

10.3 Treatments (study drug, concurrent therapies, compliance)

Duration of exposure to the study drug, number of patients with dose adjustment (dose interruptions, changes), and dose intensity will be summarized for the main period **and the study extension** period.

Significant concurrent medication and non-drug therapies administered before and after the beginning of the administration of the study drug will be summarized by preferred terms, according to ATC class of the WHO Drug Reference List.

10.4 Primary objective

The primary objective is to evaluate the efficacy of pasireotide LAR on NFPA, based on tumor volume decrease.

10.4.1 Variable

The primary efficacy variable is the proportion of patients with NFPA reaching a tumor volume decrease of at least 20% after treatment Week 24 with pasireotide LAR.

10.4.2 Statistical analysis

The proportion of patients with a decrease of at least 20% in tumor volume will be summarized in terms of incidence rates and the exact 90% confidence interval at the end of the main study for the FAS population (week 24).

10.4.3 Control of missing values / censoring / discontinuations

A patient whose tumor volume evaluation at the beginning of the study (Screening Period, baseline data) is missing will not be considered for efficacy evaluations. Only patients with baseline evaluation and at least one later evaluation will be considered for statistical analysis. All analyses will be performed with the data observed, i.e. the primary analysis (Week 24) will only be based on data from patients with both baseline and Week 24 tumor volume evaluation.

The primary endpoint analyses will be based on the cases seen, as the population is treatment-naïve (also not having undergone surgery), and 24 weeks of treatment are expected to be necessary before a significant effect is evaluated.

10.4.4 Support Analysis

A sensitivity analysis will be performed in the primary efficacy endpoint after the imputation of missing values on week 24 from the last observation carried forward (LOCF). This will be possible for patients with baseline data and at least one later value.

10.5 Secondary objectives

Analysis population

All secondary efficacy analyses will be based on the full analysis set (FAS). The safety analysis set will be used for all safety analyses.

10.5.1 Efficacy variables and analysis

The secondary efficacy endpoints are described on section 3.3.2.

The changes in mean and percent tumor volume variation from baseline to Weeks 4, 12, and 24 will be presented together with the 90% confidence interval (90% CI). If the data are in a non-normal distribution, median CI will also be generated. The incidence rate of patients with tumor volume decrease ≥ 20% and its exact CI will be reported on weeks 4 and 12.

Summary of the statistical analyses will be provided for each disease-related symptom (headache, visual disorders, fatigue, decreased libido, and specific symptoms for men and women) on each visit. Changes in baseline scores will be summarized on each visit for all symptoms.

The time to response, defined as the time from the first injection to the first evaluation in which a patient reaches a tumor volume decrease of at least ≥ 20%, will be listed for all patients. If a patient did not reach tumor response, the period of his/her last evaluation will be used as a cutoff period. For responsive patients, average time to response will be summarized.

Additionally, logistic and cox regression models may be used to explore the association between baseline characteristics and tumor response and time to tumor response. These analyses will be specified in the report analysis plan (RAP).

The frequency and percentage of patients experiencing improvement of symptoms related to tumor compression, pituitary hormone dysfunction, normalization of the alpha subunit level, [redacted] will be presented for each symptom at each period with the associated exact 90% CI.

The incidence rates of pituitary hormone dysfunction, the normalization of alpha subunit levels, and the proportion of patients with a 50% decrease in the alpha subunit level, together with the exact 90% CI will be reported at baseline and on weeks 4, 12, and 24. The alpha subunit level analyses will be performed again with the population set according to protocol and for the subgroup of patients with increased alpha subunit levels at baseline.

Hormone profiles, alpha subunit levels, [redacted] in each period in terms of frequency (N), mean, standard deviation, median, minimum, and maximum.

[redacted]

10.5.3 Safety analyses and parameters

The safety evaluation will be based mainly on frequency of adverse events (AEs), number of patients with laboratory values outside the reference ranges, and number of patients with clinically significant changes in ECGs. Other safety data (for example, vital signs and special tests) will be considered when appropriate.

10.5.3.1 Adverse events

All AEs recorded during the study will be summarized. The incidence of treatment-emergent AEs (new or worsening from baseline) will be summarized by system organ class, severity (based on CTCAE grade), type of AE, and relationship to the study drug. Deaths that may be reported as SAEs and non-fatal serious adverse events will be listed by patient and organized in the table by type of AE.

10.5.3.2 Laboratory abnormalities

All laboratory values will be converted in SI units and the severity grade will be calculated using the appropriate Common Toxicity Criteria (CTC).

The frequency of laboratory abnormalities will be shown by parameter and study day. Considerably abnormal laboratory values (new or worsening from baseline based on CTC grade) will be summarized by laboratory parameter. The tables will show the comparison between the baseline laboratory result (CTC grade) and the worst result (expressed in CTC grade) during the study. Patients with abnormal laboratory values will be mentioned and values outside the normal range will be flagged. A separate list of CTC grade 3 or 4 laboratory abnormalities will also be provided.

10.5.3.3 Other safety data

Weight, height, and vital signs will be summarized in each period, using descriptive statistics (N, mean, standard deviation, median, minimum, and maximum).

Physical examination abnormalities, ECOG performance status, radiology tests, ECGs, MRIs, and visual evaluations will be identified and listed.

10.5.4 Tolerability

Dose decreases and AEs related to the study drug, e.g., gastrointestinal disorders, glucose metabolic disorders, cardiac dysfunctions, laboratory abnormalities, infections, and injection site reactions, will be summarized by presenting counts and percentages for the safety population.

10.6 Sample Size Calculation

This study is a proof of concept. The sample size of 19 evaluable patients was selected without taking statistical power into account. The response rate (proportion of patients with tumor volume decrease ≥ 20%) of at least 10% is considered clinically significant for this patient population. Table 10.1 presents the probability that there are two or more responders for the many assumed response rates. If the actual response rate is 10%, the probability of obtaining two or more responders among the 19 patients is 58%. In this study, a 90% CI will also be obtained. Table 10.2 presents the exact 90% CI when 2 - 6 among 19 patients respond to treatment. Considering that the study dropout rate is 20%, 23 patients will be enrolled in order to obtain the 19 evaluable patients for the final analysis.

Table 10.1: Probability of ≥ 2 responders in a 19 patient sample.

assumed p	0.05	0.10	0.15	0.20	0.25	0.30
P(X ≥ 2)	25%	58%	80%	92%	97%	99%
X is assumed to have a binomial distribution with p probability						

Table 10.2: Resulting 90% CI for different numbers of responders

Responders / n	Lower confidence interval	Upper limit of the confidence interval
2 / 19	1.9%	29.6%
3 / 19	4.4%	35.9%
4 / 19	7.5%	41.9%
5 / 19	11%	47.6%
6 / 19	14.7%	53%

11 Administrative procedures

11.1 Enrollment compliance

When all inclusion / exclusion criteria are met and a patient is qualified to enter the study and when all information is entered into the eCRF, enrollment will be allowed. This will allow enrollment to be properly monitored and will ensure that the populations with each type of tumor are appropriately represented in the study.

11.2 Ethic and regulatory compliance

This clinical study was designed and must be implemented and reported according to the protocol, the Harmonized Tripartite Guideline for ICH Good Clinical Practice, the applicable local regulations (including European Resolution 2001/20/EC and U.S. Code of Federal Rules Title 21), and the ethical principles established in the Declaration of Helsinki and the Brazilian legislation.

11.3 Investigator's and REC's responsibilities

The protocol and the proposed informed consent form must have been reviewed and approved by a duly established Research Ethics Committee (REC) before the start of the study. A signed and dated statement that the protocol and informed consent form were approved by the REC must be submitted to Novartis before the start of the study. Before the start of the study, the investigator must sign a protocol signature page confirming his/her agreement to conduct the study according to these documents and all instructions and procedures found in this protocol, in addition to providing access to all pertaining data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, Novartis designees, RECs, and regulatory authorities, as required.

11.4 Informed Consent Form

Eligible patients may only be enrolled in the study after providing the written informed consent (witnessed, whenever required by law or regulation), approved by the REC or, if unable to do it, after this consent is provided by the patient's legally acceptable representative.

In cases in which the patient's representative provides the consent, the patient must be informed about the study as far as possible, considering his/her understanding. If the patient is able to understand, he/she must indicate his/her consent by personally signing and dating the written informed consent form or a separate consent form. The informed consent must be obtained before the performance of any study-specific procedures (i.e., all procedures described in the protocol). The process of obtaining the informed consent must be documented in the patient's source-documents.

Novartis will provide the investigators, in a separate document, with a proposed informed consent form following ICH GCP guidelines and regulatory requirements and considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be approved by Novartis before submission to the REC, and a copy of the approved version must be provided to the Novartis monitor after approval by the REC.

Women of childbearing potential must be informed that the use of the study drug may involve unknown risks to the fetus in case of pregnancy during the study, and must agree that, in order to participate in the study, they must meet the contraceptive requirement throughout the study. In case of any doubt that the patient will reliably comply with the treatment, he/she must not be enrolled in the study.

11.5 Protocol amendments

Any change or addition to the protocol may be performed only by means of a written protocol amendment, which must be approved by Novartis, Health Authorities, whenever required, and by the REC. Only amendments required for the safety of patients may be implemented before approval by the REC. In spite of the need for formal approval for protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient enrolled in this study, even if this action represents a protocol deviation. In such cases, Novartis must be notified about such action and the REC of the study site must be informed within 10 business days.

11.5.1 History of amendments

Amendment 1 extends the treatment schedule for patients from week 24 to week 96.

For the purpose of a reference for long-term safety and efficacy evaluation of pasireotide LAR treatment, patients benefiting from the treatment with this medication according to the evaluation by the physician in charge will be offered the opportunity to enter a 72-week extension period.

- Protocol amendment 2 includes additional liver safety measurements as a result of an internal medical review of the pasireotide studies, on visits Core - V3 (D20), V4 (D28), V4L (D48), and V5 (D56);
- Extension – E2 (D28), E3 (D48), E4 (D56), E4L (D76), and E5 (D84).

11.6 Discontinuation of the study

Participation in this study is voluntary. Research subjects may withdraw their consent. The investigator may discontinue the participation of any research subject in this study, at any time, if considered as in his/her best interest.

Novartis Biociências S. A. may discontinue the study at any time, if anything that might compromise the safety of research subjects is found. If this happens, the Hospital Ethics Committee must approve the reasons prior to discontinuation.

11.7 Supply and new supply, storage of the drug, and traceability / accountability of the study drug

Study drugs must be received by a designee at the study site, handled and stored safely and appropriately, and kept in a safe place, with access restricted only to the investigator and his/her designees. Upon receipt, pasireotide LAR must be stored according to the instructions specified in the drugs labels. Clinical supplies must be dispensed only according to the protocol.

Medication labels will be written in local language and will follow Brazilian legal requirements. These labels will include the storage conditions for the drug, but not information on the patient.

The investigator must keep an accurate record of the shipment and dispensing of the study drug in a drug accountability log. Drug accountability will be observed by the field monitor during visits to the site and upon completion of the study. The site staff will be asked to return all unused study drug and packages at the end of the study or at the time of discontinuation of the study drug.

At the end of the study and as appropriate throughout the study, the investigator will return all study drug, packages, drug labels used and unused, and a copy of the completed drug accountability log, to the Novartis monitor or to the Novartis address provided in the investigator’s binder at each site.

12 Protocol compliance

The investigators agree to dedicate due diligence to avoid protocol deviations. The investigator must not, under any circumstances, contact Novartis or its representatives, if any, monitoring the study to request approval for a protocol deviation, as no authorized deviation is allowed. If the investigator considers that a protocol deviation would improve the study conduction, it must be considered as a protocol amendment and, unless this amendment is agreed upon by Novartis and approved by the REC, it cannot be implemented. All significant protocol deviations will be recorded and reported in the eCSR.

13 Publication policy

Any formal presentation or publication of the study data will be considered as a joint publication by the investigator(s) and Novartis team. Authorship will be determined by mutual agreement, based on the number of patients enrolled. For multicenter studies, it is mandatory that the first publication be based on data from all sites, analyzed as established in the protocol by Novartis statisticians, and not by the investigators.

The investigators participating in multicenter studies agree not to submit data from one site or small groups of sites before complete publication, unless formally approved by all investigators and Novartis.

Novartis must receive copies of any communication before publication (at least 20 business days for abstracts and oral presentations and 45 business days for submission to journals). Novartis will review the communications for accuracy (thus avoiding potential discrepancies regarding the submission to health authorities), verify that confidential information is not unadvertedly disclosed, and provide any relevant supplementary information.

The investigator may be asked to sign the clinical study report, if required to be used in a registration submission to health authorities in some countries. For multicenter studies, only the principal investigator appointed by Novartis at the beginning of the study must provide any signature required.

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