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 Adenomas

STATISTICAL ANALYSIS PLAN

Version No. 1, 14th February 2017

PROTOCOL: CSOM230D2401

STUDY DRUG: Pasireotida LAR (SOM 230)

Performed by:

[redacted]

Prepared for:

NOVARTIS BIOCIÊNCIAS S.A.

[redacted]

STATISTICAL ANALYSIS PLAN (SAP)

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 Adenomas

PROTOCOLO No.: CSOM230D2401 / NCT01283542

PROTOCOL VERSION: Version No. 2.00

PROTOCOL DATE: 26-03-2012

SAP prepared by:

_____ _____/_____/_____

[redacted]

dd/mmm/yyyy

SAP reviewed by:

_____ _____/_____/_____

[redacted]

dd/mmm/yyyy

SAP reviewed and approved by:

_____ _____/_____/_____

[redacted]

dd/mmm/yyyy

NOVARTIS BIOCIÊNCIAS S.A.

Table of contents

Index of tables

1 Objectives

1.1 PRIMARY OBJECTIVE

To evaluate the effect of pasireotide LAR on the proportion of patients with clinically non-functioning pituitary adenomas (NFPAs) who achieve treatment response.

1.1.1 End-point for primary objective

Proportion of patients with NFPA who achieve tumor volume reduction of at least 20% after 24-week treatment with pasireotide LAR.

1.2 SECONDARY OBJECTIVES

- To assess the effect of pasireotide LAR on the mean change of tumor volume from baseline to Week 4, 12, 24, 48, 72 and 96.
- To assess the effect of pasireotide LAR on the percentage change of tumor volume from baseline to Week 4, 12, 24, 48, 72 and 96.
- To assess the effect of pasireotide LAR on the proportion of patients achieving tumor volume reduction of at least $\geq$20% after 4 and 12, 48, 72 and 96 weeks of treatment.
- To assess the effect of pasireotide LAR on the time to tumor response.
- To assess the effect of pasireotide LAR on the disease-related symptoms*

  *Disease-related symptoms to be evaluated: headache, visual disturbances, fatigue, decreased libido, erectile dysfunction (for males only), irregular or stopped menses (for not post-menopausal female only).

- To evaluate the effect of pasireotide LAR on pituitary function at Weeks 4, 12, 24, 48, 72 and 96.
- To evaluate the effect of pasireotide LAR on alpha subunit levels at 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 responsive (*i.e.*, patients who achieved a tumor volume reduction of at least 20% with respect the initial tumor volume).
- To assess the percentage of patients that remain with tumor volume stable during the study.

1.2.1 End-points for secondary objectives

The secondary variables are:

- Mean change of tumor volume assessed by pituitary MRI from baseline to Week 4, 12, 24, 48, 72 and 96.

- Percent change of tumor volume assessed by pituitary MRI from baseline to Week 4, 12, 24, 48, 72 and 96.
- Proportion of patients achieving tumor volume reduction 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 first injection to the first evaluation the patient achieves tumor volume reduction of at least >20%.
- Change from baseline to Week 4, 12, 24, 48, 72 and 96 in disease-related symptoms scores.
- Incidence of pituitary hormonal dysfunction at baseline and at Weeks 4, 12, 24, 48, 72 and 96.
- Proportion of patients achieving alpha subunit reduction of at least 50% at Weeks 4, 12, 24, 48, 72 and 96.
- Proportion of patients achieving normalization of alpha subunit at Weeks 4, 12, 24, 48, 72 and 96.
- Percentage of CTC (≥3) adverse events 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 laboratory abnormal values and summary of laboratory assessments.
- For extension phase: among patients who had been considered as responsive (*i.e.*, patients who achieved a reduction in tumor volume of at least 20% with respect to the initial tumor volume), assess the number and proportion of patients that remained responsive during the treatment period of extension phase (according to estimates by magnetic resonance at weeks 48, 72 and 96).
- To assess the percentage of patients who remained with tumor volume stable during the study, *i.e*. patients who maintained tumor volume with variation less than 20% with respect to the basal tumor volume (according to evaluations by magnetic resonance imaging at weeks 24, 48, 72 and 96).
- If applicable, assessing whether there was difference in response between patients using dose of 40 and 60 mg of pasireotide LAR.

2 Study design

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

Eligible patients will receive pasireotide LAR 60 mg every 28 ± 3 days for 24 weeks, during the Core Phase of the study. The study is complimented by an extension. As per treating physician' discretion, patients who have benefited from the treatment with pasireotide LAR can enter an Extension Phase where they will continue to receive pasireotide LAR 60 mg at 4-week (± 3 days) intervals for up to 2 years or until pasireotide or other effective therapy becomes commercially available or until clinical benefit is noted (whichever comes first). Dose reductions to 40 mg will be permitted based on safety issues. In case of rapid deterioration of the visual field or sudden visual loss, the patient will be discontinued from the study.

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

The design of the study and a schematic of the Core Phase and Extension Phase are presented in **Figure 1** and **Figure 2**, respectively.

Figure 1 Schematic of the Pasireotide LAR Study of NFPA: Core Phase

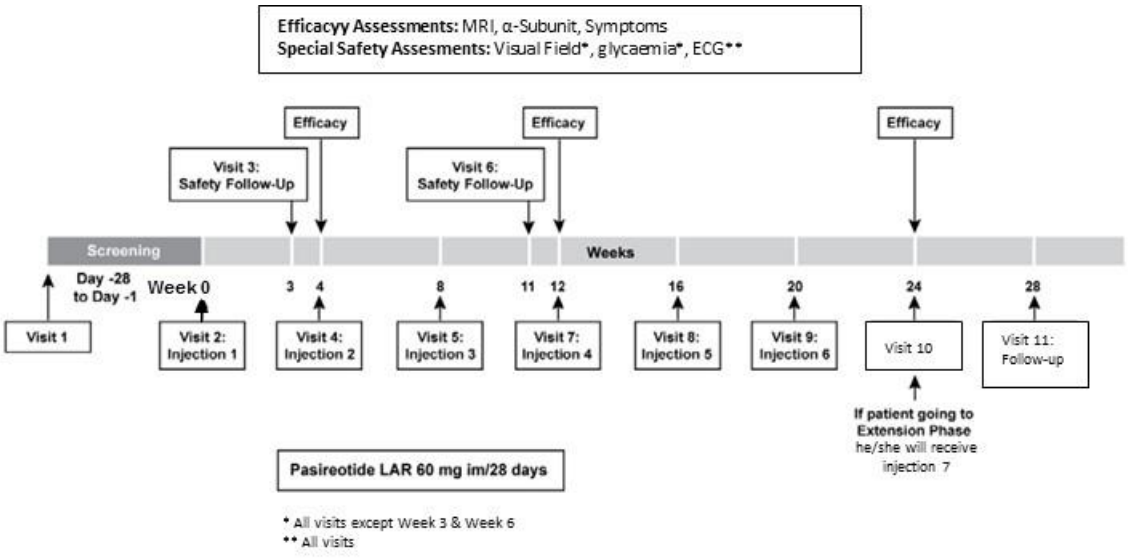
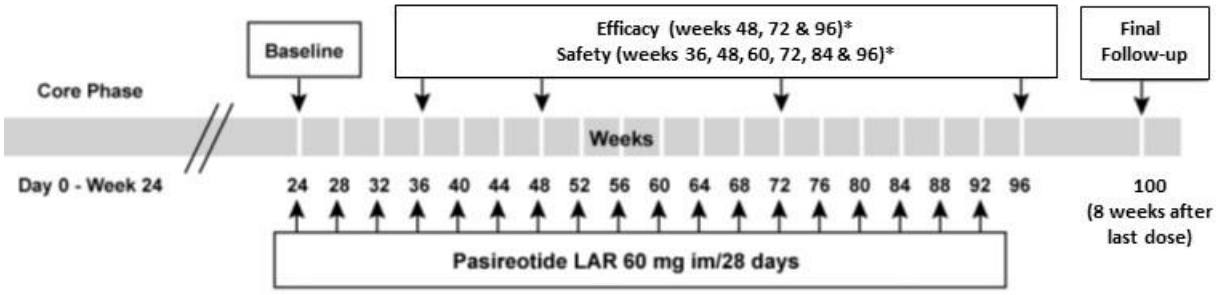


Figure 2 Schematic of the Pasireotide LAR Study of NFPA: Core Phase



*Details of efficacy and safety evaluation, presented in Table A1.

3 Population

The population for this study is adult patients with a diagnosis of NFPA who have not undergone any prior therapy (treatment-naïve) for the disease. As tumor volume changes are difficult to be evaluated in microadenomas and also because they may be misdiagnosed with incidentalomas, only patients with macroadenomas (≥ 1 cm) will be included. A total of 23 patients in 10-13 centers will be enrolled in this single-arm open-label study.

3.1 INCLUSION/EXCLUSION CRITERIA

The investigator or his/her designee must ensure that all patients who meet the following inclusion and exclusion criteria are offered enrollment in the study.

3.1.1 Inclusion criteria

1. Male or female patients ≥ 18 years.
2. Patients with clinically non-functioning pituitary macroadenomas ≥ 1 cm.
3. No previous treatment for NFPA.
4. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
5. Written informed consent obtained prior to any screening procedures.

3.1.2 Exclusion criteria

1. Patients who require a surgical intervention for relief of any sign or symptom associated with tumor compression.
2. Previous pituitary surgery.
3. Previous medical treatment for pituitary tumor.
4. Patients who have received pituitary irradiation within 10 years prior to inclusion visit (Visit 2).
5. Prolactin (PRL) levels > 100 ng/mL. (PRL evaluation should be performed with diluted samples to make sure to avoid the “hook effect.”).
6. Patients with compression of the optic chiasm causing acute clinically significant visual field defects.
7. Diabetic patients whose blood glucose is poorly controlled as evidenced by HbA1C >8%. Diabetic patients whose blood glucose is poorly controlled as evidenced by HbA1C >8%. Patients with a known history of impaired fasting glucose or diabetes mellitus with HbA1c <8% may be included; however, blood glucose and anti diabetic treatment must be monitored closely throughout the trial and adjusted as necessary.
8. Patients with known disease of the bile duct or gallbladder, acute or chronic pancreatitis (patients with asymptomatic cholelithiasis and asymptomatic dilatation of the bile duct may be included).
9. Patients with abnormal coagulation (PT and/or APTT elevated by 30% above normal limits) or patients receiving anticoagulants that affect PT (prothrombin time) or APTT (activated partial thromboplastin time).
10. Patients who have congestive heart failure (NYHA Class III or IV), unstable angina, sustained ventricular tachycardia, ventricular fibrillation, advanced heart block or a history of acute myocardial infarction within the 24 weeks preceding enrolment visit (Visit 2).

11. Screening (Visit 1) or baseline (predose, Visit 2) QTcF > 450 msec.
12. History of syncope or family history of idiopathic sudden death.
13. Sustained or clinically significant cardiac arrhythmias.
14. Risk factors for Torsades de Pointes such as uncorrected hypokalemia, uncorrected hypomagnesemia, cardiac failure, clinically significant/symptomatic bradycardia or high grade AV block.
15. Concomitant disease(s) that could prolong the QT interval such as autonomic neuropathy (caused by diabetes or Parkinson's disease), HIV, cirrhosis, uncontrolled hypothyroidism or cardiac failure.
16. Patients who are taking medication(s) known to increase the QT interval.
17. Patients with liver disease such as cirrhosis, chronic active B or C hepatitis or chronic persistent hepatitis, or patients with ALT and/or AST more than 2 x ULN, serum bilirubin > 1.5 ULN, serum albumin < 0.67 x LLN.
18. Patients with serum 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 prior medical condition that, in the judgment of the investigator may interfere with the conduct of the study or the evaluation of the study results.
21. History of immunocompromise, including a positive HIV test result (ELISA and Western blot). A HIV test will not be required; however, previous medical history will be reviewed.
22. Known hypersensitivity to somatostatin analogues or any other component of the pasireotide LAR.
23. Patients with active malignant disease within the last five years (with the exception of basal cell carcinoma or carcinoma in situ of the cervix)
24. Patients with the presence of active or suspected acute or chronic uncontrolled infection
25. Female patients who are pregnant or lactating, or are of childbearing potential and not practicing a medically acceptable method of birth control. If a woman is participating in the trial then one form of contraception is sufficient (pill or diaphragm) and the partner should use a condom. If oral contraception is used in addition to condoms, the patient must have been practicing this method for at least two months prior to the enrollment and must agree to continue the oral contraceptive throughout the course of the study and for 3 months after the study has ended. Male patients who are sexually active are required to use condoms during the study and for three month afterwards as a precautionary measure (available data do not suggest any increased reproductive risk with the study drugs)
26. Participants in investigational drug study 30 days before enrolment visit (Visit 2). Patients must have recovered from all side effects of other investigational therapy.
27. History of non-compliance to medical regimens, or patient who is considered potentially unreliable, or any circumstance at the time of study inclusion that would preclude completion of the entire study or the required follow up .
28. Patients who have a history of alcohol or drug abuse in the 12 month period prior to Visit 1 (Screening).
29. Presence of the surface antigen of hepatitis B (HBsAg).
30. Presence of the antibody test for hepatitis C virus (anti- HCV).
31. Patients who have undergone major surgery/surgical therapy for any cause within 4 weeks prior to randomization.
32. Patients with confirmed hypothyroidism, hypoadrenalism, and hypogonadism (except physiologic menopause and andropause), unless they are adequately treated with stable doses of hormone replacement therapy for a minimum of 3 months prior to study entry .
33. Patients in use of growth hormone replacement .
34. Uncontrolled cardiovascular, kidney, or metabolic disorders.
35. Serious neurologic or psychiatric disorders.

36. Contraindication to MRI such as (but not limited to): cerebral aneurysm clips, cardiac pacemaker, retained cardiac pacemaker wire and temporary pacemaker, cochlear implants, hearing aids that contain internal and non-removable parts, Swan-Ganz catheter, aortic balloon, aortic prosthesis type Zenith AAA Endovascular Graft, other possible contraindications related to ferromagnetic material identified in the patient interview.

4 Visit schedule and assessments

Table A 1 and **Table A 2** list all of the assessments for the Core Phase and Extension Phase, respectively, and indicates with an "X" the visits when they will be performed. All data obtained from these assessments must be supported in the patient's source documentation. The table indicates which data are entered into the database (D) or remain in source documents only (S). Assessments that generate data for database entry and which are recorded on eCRFs are listed using the eCRF name.

Table A 1: Visit Schedule and Assessments for Core Study

Visit number	1	2	3	4	V401[E] 48	5	6	7	8	9	10 TDE[3]	11 FU Visit
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
Week of treatment		Enrolment	Week 3	Week 4	Week 7	Week 8	Week 11	Week 12	Week 16	Week 20	Week 24	Week28
	Screening[2]	Baseline/ Injection 1	Safety only	Injection 2	Safety only	Injection 3	Safety only	Injection 4	Injection 5	Injection 6	Injection 7# (if patient will join the Extension Phase)	Safety FU
Informed consent (S)	X											
Demography (D)	X											
Diagnosis and extent of disease (D)	X											
Relevant medical history/ current medical conditions (D)	X											
Inclusion/exclusion criteria check (S)	X											
Vital signs (D)	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam (S)	X	X	X	X	X	X	X	X	X	X	X	X

Height (D)	X											
Weight (D)	X	X	X	X	X	X	X	X	X	X	X	X
Symptom assessment/ Disease-related symptoms [4] (D)	X	X	X	X	X	X	X	X	X	X	X	
ECOG performance status (D)	X	X	X	X		X	X	X	X	X	X	X
ECG [14] (D)	X	X	X	X		X	X	X	X	X	X	
Serum pregnancy test [5,6]	X							X			X	
Hematology (BD)	X			X		X		X	X	X	X	
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] (D)	X			X		X		X	X	X	X	
Fasting Blood Glucose, Insulin [6]	X			X		X		X	X	X	**X**	
HbA1c [6]	X							X			X	
Biochemistry [6,8] (D)	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 anit-HCV (D)	X											

Vitamin B12, folic acid [6]	X										X	
Hormonal evaluation [6, 9] (D)	X			X				X			X	
Alpha subunit evaluation [6]	X			X				X			X	
Visual field (camp) evaluation [10] (D)	X	X[10]		X		X		X	X	X	X	
Gallbladder ultrasound (D) [15]	X										X	
Pituitary MRI / *Sella turcica*[15]	X			X				X			X	
Adverse events (D)		X	X	X	X	X	X	X	X	X	X	
Pasireotide LAR administration (D)		X		X		X		X	X	X	X[#]	
Prior/Concomitant medications [11] (D)	X	X	X	X	X	X	X	X	X	X	X	
Study completion[13] (D)												X[13]

Pasireotide dose on this visit will be administered to selected patients, as per physician discretion, if the patient will be included in the Extension Phase based on response assessed by investigator/ benefit with the drug.

[1] Will be allowed a window of ± 3 days for the planned visitsand assessments, unless otherwise specified.

[2] It will be allowed a window of ± 3 days for the planned visits and assessments, unless indicated otherwise.

[3] To be completed prior to study drug administration

[4] To be completed if the patient discontinues prematurely or at study completion.

[5] Disease related symptoms that will be evaluated: headache, visual disturbances, fatigue, decreased libido, erectile dysfunction (for males only), irregular or stopped menses (for not post-menopausal female only). The investigator will also ask the patient to score the symptoms according to a five-point score scale (0=absent, 1=mild, 2=moderate, 3=severe, 4=very severe). The others will be assessed as present or absent.

[6] Serum pregnancy test will be performed in the final follow-up visit if patient report menstrual delay or as per physician discretion.

[7] Blood and urine to be collected prior to study drug administration. Pts should be fasting for 12 hours.

[8] Hematology and Coagulation include: Hemoglobin, hematocrit (HCT), WBC count with differential, RBC Count with differential and platelet count; PT and APTT.

[9]Complete biochemistry includes: total cholesterol, low density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, calcium, phosphorus, chloride, sodium, potassium, inorganic phosphorus, creatinine, urea/BUN, uric acid, CPK, LDH, alkaline phosphatase, δ-GT, total protein, albumin, SGOT, SGPT, total bilirubin. If the total bilirubin concentration is increased above 2.0 times the upper normal limit, total bilirubin should be differentiated into the direct and indirect reacting bilirubin at visits.

[10] Hormonal evaluation (serum)—pituitary disease assessments: testosterone (for male), estradiol (for female), prolactin, free T4, TSH, LH, FSH, GH, IGF-I, cortisol, ACTH, a-subunit. If the evaluation of the visual field in the selection is performed within 14 days prior to Visit 2, it can be considered as the baseline and there is no need to repeat it for Visit 2.

[11] Assess with standard automated perimetry (SAP). It is suggested Humphrey Field Analyzer. The window to perform SAP should be no more than 7 days before the scheduled visit.

[12] Prior and concomitant medication cover any therapy including chemotherapy, radiotherapy and surgery or medication received in past or ongoing treatment.

[13] All medications/therapies used to treat the tumor/symptoms under this study given to a patient ≤ 4 weeks after the last dose of study treatment must be recorded in the e-CRF. All patients will be followed for safety for 56 days from the last dose of study medication.

[14] The safety follow-up has to be performed 56 ± 3 days after the patient received the last pasireotide LAR dose. For patients continuing into the extension study this visit will not be performed after the end of the main study but 56 ± 3 days after the patient has finished extension study.

[15] ECG will be performed prior to the drug administration. In Visit 3 (Day 20) and Visit 6 (Day 76), ECG will be done independent of drug administration.

[16] The window to perform MRI and gallbladder US should be no more than 7 days before the scheduled visit.

[17] If patient will not be assigned for Extension Phase, follow-up visit will be Visit 11.

Table A 2: Visit Schedule and assessments for extension study

Visit	10[1]	11	12	402	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28 TDE	29 FU[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 (D)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Current medical conditions (D)	X				X			X			X			X			X			X	X
Vital signs (D)	X				X			X			X			X			X			X	X
Physical exam (S)	X				X			X			X			X			X			X	X
Weight (D)	X				X			X			X			X			X			X	X
MRI / *sella turcica*	X							X						X						X	
Alpha subunit [2]	X							X						X						X	
ECG (D)	X				X			X			X			X			X			X	
Gallbladder ultrasound (D)	X							X												X	
ECOG *Performance status* (D)	X				X			X			X			X			X			X	X
Symptom assessment/ Disease related symptoms (D)	X				X			X			X			X			X			X	
Serum pregnancy test [2,10]	X							X						X						X	
Hematology (D)	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] (D)	X							X						X						X	

Fasting blood glucose and insulin [2]	X							X						X						X	
HbA1c[2]	X							X						X						X	
Biochemestry[2,4]	X							X						X						X	
LFTs (ALT, AST, total bilirubin, albumin, ALP, γ-GT) (D)	X			X				X						X						X	
Hormonal evaluation[2,5](D)	X							X						X						X	
Visual field evaluation[6]	X							X						X						X	
Vitamin B12, folic acid [2]	X							X												X	
Pariseotide LAR Admin[7] (D)	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Prior/Concomitant Meds[8] (D)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Study completition[9] (D)																					X

[1] Patients will be invited to participate in the extension phase, according to the opinion of the treating physician, if they are benefiting from treatment with pasireotide LAR

[2] Blood and urine to be collected prior to study drug administration. Patients should be fasting for 12 hours.

[3] Hematology and coagulation include: hemoglobin, hematocrit (Hct), WBC count with differential, RBC count with differential and platelet count, PT, and APTT.

[4] Complete biochemistry includes: total bilirubin, total cholesterol, LDL, HDL, triglycerides, creatinine, urea, uric acid, δ-GT, total protein, albumin, AST, ALT, CPK, LDH alkaline phosphatase , sodium, potassium , inorganic phosphorus , and calcium chloride. If the total bilirubin concentration is increased above 2.0 times the upper normal limit, total bilirubin should be differentiated into the direct and indirect reacting bilirubin.

[5] Hormonal evaluation (serum)—pituitary disease assessments: testosterone (for male), estradiol (for female), prolactin, free T4, TSH, LH, FSH, GH, IGF-1, cortisol, ACTH.

[6] Assess with standard automated perimetry (SAP). It is suggested Humphrey Field Analyzer. The window to perform SAP should be no more than 7 days before the scheduled visit.

[7] Patients will continue to receive pasireotide LAR i.m. every 28 (± 3) days. The drug administration will be performed by a health care professional in the site. The last dose administration is in Week 92 (Visit 27).

[8] All medications/therapies used to treat the tumor/symptoms under this study given to a patient ≤ 4 weeks after the last dose of study treatment must be recorded in the eCRF. All patients will be followed for safety for 56 ± 3 days days from the last dose of study medication.

[9] The safety follow-up visit (Visit 29) has to be performed 56 ± 3 days after the patient received the last pasireotide LAR dose.

[10] Serum pregnancy test will be performed in the final follow-up visit if patient report menstrual delay or as per physician discretion

.

5 Statistical methods and data analysis

The following sections describe the analyses to be conducted.

For the Core Period of the study, efficacy and safety analyses will be conducted on the data collected by the time when all the enrolled patients have completed their EOS Visit. All the formal safety follow-up data of those patients who did not enter the extension study will also be included in the core study safety analyses. A final analysis will be completed when all the patients in the Extension complete their last visit and will be reported in either an additional clinical study report or in an addendum to the core study report.

Other additional data prior to the end of the Core Phase of the trial will be analyzed and then summarized in an additional report of clinical study or in a major study report.

Novartis or designated CRO will analyze all data using the SAS System for data analysis 9.4 . Any data analyses carried out independently by an investigator should be submitted to Novartis before publication or presentation.

The data from all centers participating in the trial will be combined, so that an adequate number of patients will be available for analysis. The statistical analysis methods described in this section will focus on the analysis of the data in the core study. Similar methods will be applied to the analyses in the Extension Phase as appropriate.

5.1 POPULATIONS FOR ANALYSIS

Full analysis set (FAS): consists of all patients who successfully completed the screening and have received at least one dose of study medication. FAS will be the primary set for all efficacy analyses.

Safety analysis set: consists of all patients who received at least one dose of study drug and had at least one post-baseline safety assessment.

Note the statement that a patient had no AEs (on the Adverse Event e-CRF) constitutes a safety assessment. The safety set will be used for all safety analyses.

The analyzes presented in this section represent the analyzes that will be used for the Core Phase of the trial. A final analysis will be performed when all patients of Extension Phase completed their last visit and will be reported or as additional clinical study report or as an addendum to the Core Phase of the trial report.

5.2 PATIENT DEMOGRAPHICS/OTHER BASELINE CHARACTERISTICS

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

5.3 TREATMENTS (STUDY DRUG, CONCOMITANT THERAPIES, COMPLIANCE)

The duration of exposure to the study drug, number of patients with dose adjustment (i.e., interruptions, dose changes) and dose intensity will be summarized based on FAS for core and extension period of the study.

Concomitant medications and significant non-drug therapies prior to and after the start of the study drug will be summarized by preferred terms according to the ATC class of the WHO Drug Reference List.

5.4 PRIMARY OBJECTIVE

The primary objective is to assess the efficacy of pasireotide LAR in NFPA based on tumor volume reduction.

5.4.1 Variable

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

5.4.2 Statistical Analysis

Proportion of patients with at least 20% of reduction in tumor volume will be summarized in terms of incidence rates and exact 90% confidence interval at end of core period of the study for FAS population (Week 24).

5.4.3 Handling of missing values/censoring/discontinuations

A patient whose tumor volume assessment at baseline (Visit 1) is missing will not be considered for the efficacy assessments. Only those patients will be considered for analysis for which baseline and at least one post baseline records are reflecting non missing values. All the analysis will be performed with as observed data i.e. the primary analysis (Week 24) will be based on only patients that have both baseline and Week 24 tumor volume assessment.

The analysis of the primary endpoint will be based on observed cases since the patients population is naive (including not having any surgery) and it is expected that 24 weeks of treatment is needed before meaningful effect are assessed.

5.4.4 Supportive analyses

A sensitivity analysis will be performed on primary efficacy endpoint after imputing the week 24 missing values by last observed carried forward (LOCF) technique, for patients having baseline and at least one post baseline value.

5.5 SECONDARY OBJECTIVES

Population for the analysis

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

5.5.1 Efficacy variables and analysis

The secondary efficacy endpoints are described in section 1.2.1.

The mean and percent change in tumor volume from baseline to Week 4, 12 and 24 will be presented along with the 90% confidence interval (CI). If data is found to be skewed, CIs for median will also be generated. Incidence rates for patients with ≥ 20% reduction in tumor volume and its exact CI will be reported at Week 4 and 12.

Summary statistics will be provided for each disease related symptoms (headaches, visual disturbance, fatigue, symptoms specific to man and woman) at each visits. Change from baseline scores will be also summarized at each visit for all symptoms.

Time to response, defined as time from the first injection to first evaluation where patient achieve tumor volume reduction of at least ≥ 20%, will be listed for all patients. If a patient has not achieved tumor response, the time of last assessment will be indicated as censoring time.

Kaplan-Meier analysis will be performed for time to response aiming to compute the median time to response and corresponding 95% confidence interval. Cox regression exploratory analysis will be used to estimate the hazard ratio with corresponding 95% confidence intervals for time to tumor volume reduction of at least ≥ 20% as a function of baseline characteristics (duration of disease, dose at V2, dose reduction, visual field (abnormal/normal), [redacted] and α subunit at V1).

Logistic regression will be performed to explore association between baseline characteristics and tumor response.

Frequency and percentage of patients who present improvement of symptoms related to tumor compression, pituitary hormonal dysfunction, alpha subunit level normalization, [redacted] will be presented for each symptom at each time point with associated exact 95% CI.

Incidence rates of pituitary hormonal dysfunction, normalization of alpha subunit level and proportion of patients with 50% reduction in alpha subunit level along with its exact 95% CI will be reported at baseline, Week 4, 12 and 24. Analyses for alpha subunit level will be repeated with per protocol population set and for the subgroup of patients with elevated alpha subunit level at baseline.

Hormone profiles, alpha subunit levels and [redacted] will be summarized at each time point in terms of frequency (N), mean, standard-deviation, median, minimum, and maximum.

5.5.3 Safety parameters and analyses

The assessment of safety will be based mainly on the frequency of adverse events (AEs), on the number of patients with laboratory values that fall outside of reference ranges and the number of patients with clinically notable ECG data. Other safety data (e.g vital signs, special tests) will be considered as appropriate.

5.5.3.1 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 grades), type of AE, relation to the study drug. Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of AE.

Treatment-emergent adverse events (TEAEs) will include all adverse events who started between first and 28 days after the last administration of study medication.

5.5.3.2 Laboratory abnormalities

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

Frequency of laboratory abnormalities will be displayed by parameter and study day. Notably abnormal laboratory values (new or worsening from baseline based on CTC grades) will be summarized by laboratory parameter. Shift tables will be presented comparing baseline laboratory result (CTC grade) with the worst result (expressed in CTC grade) during study. Patient with abnormal laboratory values will be listed and values outside the normal ranges will be flagged. A separate listing of laboratory abnormalities of CTC grade 3 or 4 will also be provided.

5.5.3.3 Other safety data

Weight, height and vital signs will be summarized at each time point using descriptive statistics (N, mean, standard-deviation, median, minimum, and maximum).

Abnormalities of physical examination, ECOG performance status, radiological examinations, ECG, MRI, and visual evaluations will be identified and listed.

5.5.4 Tolerability

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

5.6 SAMPLE SIZE RATIONAL

This is a proof of concept study. The sample size of 19 evaluable patients was selected without regard for statistical power. A response rate (proportion of patients with tumor volume reduction ≥ 20%) of at least 10% is considered clinically meaningful for this patient population. **Table A 3**, presents for various assumed response rates the probability of having two or more responders. If the true response rate is 10%, the probability of getting two or more responders out of 19 patients is 58%. In this trial the 90% CI will also be obtained. **Table A 4,** presents the exact 90% CI when 2-6 patients respond out of the 19 patients. Considering the dropout of 20%, we will enrol 23 patients to get 19 evaluable patients for final analysis.

Table A 3: Probability of getting ≥ 2 response in a sample of 19 patients

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 binomial distribution with probability p						

Table A 4: Resulting 90% CIs for various number of observed responders

Responders/n	Lower confidence limit	Upper confidence limitl
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%

6 Study Results

The study results are presented in Appendix 1: Statistical Tables – Core study phase.

The extension study results are presented in Appendix 2: Statistical Tables – Extension study.

7 Clarifications to the study protocol

The following clarifications to the study protocol were considered on this SAP:

- Clarification of statistical analysis for time to response and baseline characteristics
- Definition of treatment-emergent adverse events
- Definition of comparative analysis of hormonal parameters
- Confidence interval of 95% instead of 90% due to the standard approach in clinical epidemiology

Any deviations from methodology/definitions/analysis described on this SAP should be previously accepted by the sponsor and documented (together with reasoning, if relevant) in the statistical analysis report.

Appendix 1: Statistical Tables – Core study phase

Table 1 – Patients' disposition

	Total (n=xx)
Patients eligible for study treatment, n (%)	
Yes	
No	
Inclusion criteria	
Exclusion criteria	
Other	
Total	
Treatment duration completed as per protocol, n (%)	
Yes	
No	
Total	
Primary reason for end of treatment, n (%)	
Adverse Event(s)	
Subject withdrew consent	
Lost to follow-up	
Administrative problems.	
Death	
Disease progression	
Subject is unable to tolerate the minimum pasireotide LAR dose of 40 mg.	
Acute or progressive vision loss confirmed by a new visual field evaluation.	
Pregnancy	
Uncontrolled diabetes mellitus.	
Clinically significant abnormal test procedure result(s).	
Clinically significant abnormal laboratory value(s)	
Protocol deviation	
Investigator's decision	
Other	
Study populations, n (%)	
FAS	
Safety	

Table 2 – Demographics – FAS population

	Total (n=xx)
Gender, n (%)	
Male	
Female	
Childbearing potential	
Non-childbearing potential	
Total	
Age (years)	
N	
Mean	
Median	
Standard Deviation	
Minimum	
Maximum	
Race, n (%)	
White / Caucasian ancestry	
Black/ / African ancestry	
Native ancestry	
Asian ancestry	
Other	
Total	
Height (cm)	
N	
Mean	
Median	
Standard Deviation	
Minimum	
Maximum	
Weight (kg)	
N	
Mean	
Median	
Standard Deviation	
Minimum	
Maximum	
BMI (Kg/m^2)	
N	
Mean	
Median	
Standard Deviation	
Minimum	
Maximum	

Table 3 – Medical history – FAS population

	Total (n=xx)
Duration of disease (years)[a)]	
N	
Mean	
Median	
Standard Deviation	
Minimum	
Maximum	
Medical history or current medical condition prior to first study drug administration, n (%)	
Yes	
No	
Total	

a) The difference between the initial visit and the date of diagnosis of pituitary adenocarcinoma, in years.

Table 4 – Concomitant medication

	Total (n=xx)
Any medication or significant non-drug therapy, n (%)	
Yes	
No	
Total	
Concomitant medication for hormone replacement, n (%)	
Yes	
No	
Total	

Table 5 – HbA1c, fasting blood insulin and glucose at visit 1 – FAS population

	Total (n=xx)
HbA1c performed, n (%)	
Yes	
No	
Total	
HbA1c (%)	
N	
Mean	
Median	
Standard Deviation	
Minimum	
Maximum	
Normal	
Abnormal	
Clinically significant	
Non-clinically significant	
HbA1c ≤7%	
Yes	
No	
Total	
Fasting blood insulin (ulU/mL), n (%)	
Yes	
No	
Total	
Fasting blood insulin (ulU/mL)	
N	
Mean	
Median	
Standard Deviation	
Minimum	
Maximum	
Normal	
Abnormal	
Clinically significant	
Non-clinically significant	
Fasting blood glucose (mg/dL), n (%)	
Yes	
No	
Total	
Fasting blood glucose (mg/dL)	
N	
Mean	
Median	
Standard Deviation	
Minimum	
Maximum	
Normal	
Abnormal	
Clinically significant	
Non-clinically significant	

Table 6 – Treatment – FAS population

	Total (n=xx)															
	V2		**V4**		**V5**		**V7**		**V8**		**V9**		**V10**		**Core phase**	
Study medication administered, n (%)																
Yes															-	-
No															-	-
Total															-	-
Dose, n (%)																
60 mg															-	-
40 mg															-	-
Total															-	-
Dose adjustment, n (%)																
Yes	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
No	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Total	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Exposure (days)[a)]																
N	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Mean	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Median	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Standard	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Minimum	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Maximum	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Mean administration dose (mg)[b)]																
N	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Mean	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Median	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Standard	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Minimum	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Maximum	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Dose reduction before tumor volume reduction of at least 20%																
Yes																
No																
Total																

a) The difference between the last administration and the first administration, in days.
b) Cumulative dose (total dose administered) divided by number administrations.

Table 7 – Magnetic resonance imaging – FAS population

	Total (n=xx)							
	V1	**V4**	**95%CI**	**V7**	**95%CI**	**V10**	**95%CI**	
Volume (cm^3)								
N			-		-		-	
Mean			-		-		-	
Median			-		-		-	
Standard			-		-		-	
Minimum			-		-		-	
Maximum			--		--		--	
Tumor is not			-		-		-	
Missing values			-		-		-	
Volume change[a] (cm^3)								
N	-							
Mean	-							
Median	-							
Standard	-							
Minimum	-							
Maximum	-							
Percentage change in volume[a] (%)								
N	-							
Mean	-							
Median	-							
Standard	-							
Minimum	-							
Maximum	-							
Reduction of tumor volume[b], n (%)								
Yes								
No								
≥20% tumor volume reduction[c], n (%)								
Yes	-	-						
No	-	-		-		-		-
Total	-	-		-		-		-
≥20% tumor volume reduction using LOCF method, n (%)								
Yes	-	-	-	-	-	-	-	-
No	-	-	-	-	-	-	-	-
Total	-	-	-	-	-	-	-	-

95%CI: 95% confidence interval.
a) The difference between visit i and V1.
b) For reduction='yes' will be considered all patients who obtained 'volume in visit i – volume in V1' >0.
c) For reduction ≥20%='yes' will be considered all patients who obtained 'Percentage change in volume at visit i' ≥20.

Table 8 – Time to response – FAS population

	Total (n=xx)	
	Statistics	**95% CI**
Time to response		
N		
Censored		
Events (Reduction ≥20% in tumor volume)		
Mean		
Median		
25th Percentile		
75th Percentile		
Range		

$CI_{95\%}$: 95% confidence interval.
Time between first administration and first date of reduction ≥20% in tumor volume.

Figure 3 – Kaplan-Meier curve for time to response – FAS population

Table 9 – Time to response versus baseline characteristics– FAS population

Time to response [a]	**Total n=(xx)**			
	Statistics	**$CI_{95\%}$**	**Statistics**	**$CI_{95\%}$**
Visual field at baseline	**Normal**		**Abnormal**	
Time to response [a]				
N				
Censored				
Events (progression or death)				
Mean				
Median				
25th Percentile				
75th Percentile				
Range				
Hazard ratio [b]				
p-value				
Dose at V2	**60 mg**		**40mg**	
Time to response [a]				
N				
Censored				
Events (progression or death)				
Mean				
Median				
25th Percentile				
75th Percentile				
Range				
Hazard ratio [b]				
p-value				
Dose reduction before response	**Yes**		**No**	
Time to response [a]				
N				
Censored				
Events (progression or death)				
Mean				
Median				
25th Percentile				
75th Percentile				
Range				
Hazard ratio [b]				
p-value				
Duration of disease (years)				
Hazard ratio [b]				
p-value				
[redacted]				
α subunit at V1				
Hazard ratio [b]				
p-value				

$CI_{95\%}$: 95% confidence interval.

Time between first administration and first date of reduction ≥20% in tumor volume.

[a] Kaplan-Meier estimates.

[b] Cox regression estimates.

Table 10 – Disease-related symptoms – FAS population

	Total (n=xx)									
	V1	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Headache[a)], n (%)										
Absent										
Mild										
Moderate										
Severe										
Very severe										
Total										
Improved, n (%)										
Yes	-	-								
95%CI										
No	-	-								
Total	-	-								
Visual disturbances[a)], n (%)										
Absent										
Mild										
Moderate										
Severe										
Very severe										
Total										
Improved, n (%)										
Yes	-	-								
95%CI										
No	-	-								
Total	-	-								

Table 10 (Cont.) – Disease-related symptoms – FAS population

	Total (n=xx)									
	V1	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Fatigue [a], n (%)										
Absent										
Mild										
Moderate										
Severe										
Very severe										
Total										
Improved, n (%)										
Yes										
95%CI										
No										
Total										
Erectile dysfunction[b], n(%)										
Yes										
No										
Total										
Improved, n (%)										
Yes	-	-								
95%CI										
No	-	-								
Total	-	-								

Table 10 (Cont.) – Disease-related symptoms – FAS population

	Total (n=xx)									
	V1	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Regular menses[c], n (%)										
Yes										
No										
Total										
Improved, n (%)										
Yes	-	-								
95%CI										
No	-	-								
Total	-	-								

a) For each symptom, it will considered as improvement if the severity reduce at least one point (eg. 'Severe' at v_1 and 'moderate' at v_i will be considered as improvement in vi).
b) For patients who registered 'No' in V_1 and 'Yes' in v_i it will be considered as an improvement in v_i.
c) For patients who registered 'No' in V_1 and 'Yes' in v_i it will be considered as an improvement in v_i.

Table 11 – [redacted] Alpha-subunit – FAS population

Table 11 (Cont.) – [redacted] Alpha-subunit – FAS population

	Total (n=xx)					
	V1	V4	V7	95%CI	V10	95%CI
α subunit (ng/mL)						
N				-		-
Mean				-		-
Median				-		-
Standard Deviation				-		-
Minimum				-		-
Maximum				-		-
Normal				-		-
Abnormal				-		-
CS				-		-
NCS				-		-
Reduction of α subunit ≥50%[c], n (%)						
Yes	-	-				
No	-	-				
Total	-	-				

CS: Clinically significant; NCS: Not clinically significant.
95%CI: 95% confidence interval.

[redacted]

c) For reduction ≥50%='yes' will be considered all patients who obtained percentage change from baseline in α subunit at visit i' ≥50.

Table 13 – Visual field – FAS population

	Total (n=xx)							
	V1	**V2**	**V4**	**V5**	**V7**	**V8**	**V9**	**V10**
Right eye								
Normal/abnormal, n (%)								
Normal								
Abnormal								
Mild								
Severe								
Total								
Findings, n (%)								
Upper right quadrantanopia								
Upper left quadrantanopia								
Lower right quadrantanopia								
Lower left quadrantanopia								
Temporal hemianopsia								
Nasal hemianopsia								
Other								
Evolutive information, n (%)								
Stable	-	-						
Improved	-	-						
Worsened	-	-						
Total	-	-						
Left eye								
Normal/abnormal, n (%)								
Normal								
Abnormal								
Mild								
Severe								
Total								
Findings, n (%)								
Upper right quadrantanopia								
Upper left quadrantanopia								
Lower right quadrantanopia								
Lower left quadrantanopia								
Temporal hemianopsia								
Nasal hemianopsia								
Other								

Table 13 (Cont.) – Visual field – FAS population

	Total (n=xx)							
	V1	**V2**	**V4**	**V5**	**V7**	**V8**	**V9**	**V10**
Left eye								
Evolutive information, n (%)								
Stable	-	-						
Improved	-	-						
Worsened	-	-						
Total	-	-						

Table 14 – Gallblader ultrasound – FAS population

	Total (n=xx)	
	V1	**V10**
Gallblader ultrasound performed, n (%)		
Yes		
No		
Total		
If yes		
Any gallstones detected, n (%)		
Yes		
No		
Total		
Dilatation of the intra or extra hepatic ductal system, n (%)		
Yes		
No		
Total		
Location of dilatation, n (%)		
Intrahepatic ductal system		
Extrahepatic ductal system		
Total		

Table 15 – Treatment-emergent adverse events and serious adverse events – Safety population

	Total (n=xx)
Patients with at least one adverse event, n (%)[a)]	
No	
Yes	
Total	
Patients with at least one serious adverse event, n (%)[a)]	
Yes	
No	
Total	
Grade of adverse events, n (%)[b)]	
Grade 1	
Grade 2	
Grade 3	
Grade 4	
Total	
Grade ≥ 3	
Relationship of study drug, n (%)[b)]	
Not suspected	
Suspected	
Total	
Action taken for adverse event, n (%)[b)]	
No action taken.	
Study drug dosage adjusted / temporarily interrupted.	
Study drug permanently discontinued due to this adverse event	
Concomitant medication taken	
Non-drug therapy given	
Hospitalization / prolonged hospitalization	
Serious adverse events, n (%)[b)]	
Yes	
No	

a) Percentage calculated within the total number of patients of safety population (n=xx).
b) Percentage calculated within the total number of adverse events reported by safety population (n=xxx).

Table 16 – Incidence of treatment-emergent adverse events – Safety population

	Total (n=xx)
Incidence of adverse events, n (%)	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	

a) Percentage calculated for total of patients of patients of the safety population (n=xx).

Table 17 – Incidence of serious treatment-emergent adverse events – Safety population

	Total (n=xx)
Incidence of serious adverse events, n (%)	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	

a) Percentage calculated for total of patients of patients of the safety population (n=xx).

Table 18 – Incidence of treatment-emergent adverse events with suspected relationship with study drug – Safety population

	Total (n=xx)
Incidence of adverse events with suspected relationship with study drug, n (%)	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	

a) Percentage calculated for total of patients of patients of the safety population (n=xx).

Table 19 – Incidence of serious treatment-emergent adverse events with suspected relationship with study drug – Safety population

	Total (n=xx)
Incidence of serious adverse events with suspected relationship with study drug, n (%)	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	

a) Percentage calculated for total of patients of patients of the safety population (n=xx).

Table 20 – Treatment-emergent adverse events – Safety population

	Total (n=xx)
Adverse events, n (%)	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	

Percentage calculated within the total number of adverse events reported by safety population (n=xxxx).

Table 21 – Serious treatment-emergent adverse events – Safety population

	Total (n=xx)
Serious adverse events, n (%)	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	

Percentage calculated within the total number of serious adverse events reported by safety population (n=xxxx).

Table 22 – Treatment-emergent adverse events with suspected relationship with study drug – Safety population

	Total (n=xx)
Adverse events with suspected relationship with study drug, n (%)	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	

Percentage calculated within the total number of adverse events with remote, possible or probable relationship with study drug reported by safety population (n=xxxx).

Table 23 – Serious treatment-emergent adverse events with suspected relationship with study drug – Safety population

	Total (n=xx)
Serious adverse events with suspected relationship with study drug, n (%)	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	

Percentage calculated within the total number of serious adverse events with remote, possible or probable relationship with study drug reported by safety population (n=xxxx).

Table 24 – Hematology – Safety population

	Total (n=xx)									
	V1	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
RBC count ((million/mm^3)										
N										
Mean										
Median										
Standard										
Minimum										
Maximum										
Normal										
Abnormal										
CS										
NCS										
Hemoglobin (g/dL)										
N										
Mean										
Median										
Standard										
Minimum										
Maximum										
Normal										
Abnormal										
CS										
NCS										
Hematocrit (%)										
N										
Mean										
Median										
Standard										
Minimum										
Maximum										
Normal										
Abnormal										
CS										
NCS										

CS: Clinically significant; NCS: Not clinically significant.

Table 24 (Cont.) – Hematology – Safety population

	Total (n=xx)									
	V1	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
WBC count (/mm³)										
N										
Mean										
Median										
Standard										
Minimum										
Maximum										
Normal										
Abnormal										
CS										
NCS										
Eosinophils (/mm³)										
N										
Mean										
Median										
Standard										
Minimum										
Maximum										
Normal										
Abnormal										
CS										
NCS										
Neutrophils total (/mm³)										
N										
Mean										
Median										
Standard										
Minimum										
Maximum										
Normal										
Abnormal										
CS										
NCS										

CS: Clinically significant; NCS: Not clinically significant.

Table 24 (Cont.) – Hematology – Safety population

	Total (n=xx)									
	V1	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Lymphocytes (/mm³)										
N										
Mean										
Median										
Standard										
Minimum										
Maximum										
Normal										
Abnormal										
CS										
NCS										
Monocytes (/mm³)										
N										
Mean										
Median										
Standard										
Minimum										
Maximum										
Normal										
Abnormal										
CS										
NCS										
Basophils (/mm³)										
N										
Mean										
Median										
Standard										
Minimum										
Maximum										
Normal										
Abnormal										
CS										
NCS										

CS: Clinically significant; NCS: Not clinically significant.

Table 24 (Cont.) – Hematology – Safety population

	Total (n=xx)									
	V1	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Band neutrophils (/mm³)										
N										
Mean										
Median										
Standard										
Minimum										
Maximum										
Normal										
Abnormal										
CS										
NCS										
Platelet count (thousand/mm³)										
N										
Mean										
Median										
Standard										
Minimum										
Maximum										
Normal										
Abnormal										
CS										
NCS										

CS: Clinically significant; NCS: Not clinically significant.

Table 25 – Coagulation – Safety population

	Total (n=xx)						
	V1	**V2**	**V3**	**V4**	**V5**	**V6**	**V10**
PT (%)							
N							
Mean							
Median							
Standard Deviation							
Minimum							
Maximum							
Normal							
Abnormal							
CS							
NCS							
PT (seconds)							
N			-	-	-		
Mean			-	-	-		
Median			-	-	-		
Standard Deviation			-	-	-		
Minimum			-	-	-		
Maximum			-	-	-		
Normal			-	-	-		
Abnormal			-	-	-		
CS			-	-	-		
NCS			-	-	-		

CS: Clinically significant; NCS: Not clinically significant.

Table 25 (Cont.) - Coagulation – Safety population

	Total (n=xx)						
	V1	**V2**	**V3**	**V4**	**V5**	**V6**	**V10**
APTT (%)							
N							
Mean							
Median							
Standard Deviation							
Minimum							
Maximum							
Normal							
Abnormal							
CS							
NCS							
APTT (seconds)							
N			-	-	-		
Mean			-	-	-		
Median			-	-	-		
Standard Deviation			-	-	-		
Minimum			-	-	-		
Maximum			-	-	-		
Normal			-	-	-		
Abnormal			-	-	-		
CS			-	-	-		
NCS			-	-	-		

CS: Clinically significant; NCS: Not clinically significant.

Table 26 – Urinalysis – Safety population

	Total (n=xx)						
	V1	**V4**	**V5**	**V7**	**V8**	**V9**	**V10**
Specific gravity							
N							
Mean							
Median							
Standard Deviation							
Minimum							
Maximum							
Normal							
Abnormal							
CS							
NCS							
PH							
N							
Mean							
Median							
Standard Deviation							
Minimum							
Maximum							
Normal							
Abnormal							
CS							
NCS							
Glucose, n (%)							
Negative							
100 mg/dl or 5 mmol/L							
250 (+)mg/dl or 15 mmol/L							
500 (++)mg/dl or 30 mmol/L							
1000 (+++)mg/dl or 60 mmol/L							
2000 (++++) mg/dL or 110 mmol/L							
Total							
Normal							
Abnormal							
CS							
NCS							

CS: Clinically significant; NCS: Not clinically significant.

Table 26 (Cont.) – Urinalysis – Safety population

	Total (n=xx)						
	V1	**V4**	**V5**	**V7**	**V8**	**V9**	**V10**
Protein, n (%)							
Negative							
Trace							
30 (+)mg/dl or 0.3 g/L							
100 (++)mg/dl or 1.0 g/L							
300 (+++)mg/dl or 3.0 g/L							
> 2000 (++++) mg/dL or > 20 g/L							
Total							
Normal							
Abnormal							
CS							
NCS							
Blood, n (%)							
Negative or 0 ca Cells/µL							
"Non – Hemolyzed" or 10 ca Cells/µL (Trace)							
"Hemolyzed" or " Trace"							
" Small" (+) or 25 ca Cells/µL							
"Moderate" (++) or 80 ca Cells/µL							
"Large" (+++) or 200 ca Cells/µL							
Total							
Normal							
Abnormal							
CS							
NCS							
Bilirubin, n (%)							
Negative							
"Small " (+)							
"Moderate" (++)							
"Large" (+++)							
Total							
Not applicable							

CS: Clinically significant; NCS: Not clinically significant.

Table 26 (Cont.) – Urinalysis – Safety population

	Total (n=xx)						
	V1	**V4**	**V5**	**V7**	**V8**	**V9**	**V10**
Bilirubin, n (%)							
Normal							
Abnormal							
CS							
NCS							
Ketones, n (%)							
"Negative"							
"Trace" (5 mg/dl) or 0.5 mmol/L							
"Small" (15 mg/dl) or 1.5 mmol/L							
"Moderate" (40 mg/dl) or 4.0 mmol/L							
"Large" (80 mg/dl) or 8.0 mmol/L							
"Large" (160 mg/dl) or 16 mmol/L							
Total							
Normal							
Abnormal							
CS							
NCS							
Leukocytes, n (%)							
Negative or 0 ca Cells/µL							
"Trace" or 15 ca Cells/µL							
" Small" (+) or 70 ca Cells/µL							
"Moderate" (++) or 125 ca Cells/µL							
"Large" (+++) or 500 ca Cells/µL							
Total							
Not applicable							
Normal							
Abnormal							
CS							
NCS							

CS: Clinically significant; NCS: Not clinically significant.

Table 27 – Biochemistry – Safety population

	Total (n=xx)						
	V1	**V4**	**V5**	**V7**	**V8**	**V9**	**V10**
Urea (mg/dL)							
N							
Mean							
Median							
Standard Deviation							
Minimum							
Maximum							
Normal							
Abnormal							
CS							
NCS							
Creatinine (mg/dL)							
N							
Mean							
Median							
Standard Deviation							
Minimum							
Maximum							
Normal							
Abnormal							
CS							
NCS							
Uric acid (mg/dL)							
N							
Mean							
Median							
Standard Deviation							
Minimum							
Maximum							
Normal							
Abnormal							
CS							
NCS							

CS: Clinically significant; NCS: Not clinically significant.

Table 27 (Cont.) – Biochemistry – Safety population

	Total (n=xx)						
	V1	**V4**	**V5**	**V7**	**V8**	**V9**	**V10**
CPK (U/L)							
N							
Mean							
Median							
Standard Deviation							
Minimum							
Maximum							
Normal							
Abnormal							
CS							
NCS							
LDH (U/L)							
N							
Mean							
Median							
Standard Deviation							
Minimum							
Maximum							
Normal							
Abnormal							
CS							
NCS							
Total protein (mg/dL)							
N							
Mean							
Median							
Standard Deviation							
Minimum							
Maximum							
Normal							
Abnormal							
CS							
NCS							

CS: Clinically significant; NCS: Not clinically significant.

Table 27 (Cont.) – Biochemistry – Safety population

	Total (n=xx)						
	V1	**V4**	**V5**	**V7**	**V8**	**V9**	**V10**
Total cholesterol (mg/dL)							
N							
Mean							
Median							
Standard Deviation							
Minimum							
Maximum							
Normal							
Abnormal							
CS							
NCS							
Low density lipoprotein (LDL) cholesterol (mg/dL)							
N							
Mean							
Median							
Standard Deviation							
Minimum							
Maximum							
Normal							
Abnormal							
CS							
NCS							
High-density lipoprotein (HDL) cholesterol (mg/dL)							
N							
Mean							
Median							
Standard Deviation							
Minimum							
Maximum							
Normal							
Abnormal							
CS							
NCS							

CS: Clinically significant; NCS: Not clinically significant.

Table 27 (Cont.) – Biochemistry – Safety population

	Total (n=xx)						
	V1	**V4**	**V5**	**V7**	**V8**	**V9**	**V10**
Triglycerides (mg/dL)							
N							
Mean							
Median							
Standard Deviation							
Minimum							
Maximum							
Normal							
Abnormal							
CS							
NCS							
Sodium (mEq/L)							
N							
Mean							
Median							
Standard Deviation							
Minimum							
Maximum							
Normal							
Abnormal							
CS							
NCS							
Potassium (mEq/L)							
N							
Mean							
Median							
Standard Deviation							
Minimum							
Maximum							
Normal							
Abnormal							
CS							
NCS							

CS: Clinically significant; NCS: Not clinically significant.

Table 27 (Cont.) – Biochemistry – Safety population

	Total (n=xx)						
	V1	**V4**	**V5**	**V7**	**V8**	**V9**	**V10**
Calcium (mg/dL)							
N							
Mean							
Median							
Standard Deviation							
Minimum							
Maximum							
Normal							
Abnormal							
CS							
NCS							
Phosphorus (mg/dL)							
N							
Mean							
Median							
Standard Deviation							
Minimum							
Maximum							
Normal							
Abnormal							
CS							
NCS							
Chloride (mEq/L)							
N							
Mean							
Median							
Standard Deviation							
Minimum							
Maximum							
Normal							
Abnormal							
CS							
NCS							

CS: Clinically significant; NCS: Not clinically significant.

Table 27 (Cont.) – Biochemistry – Safety population

	Total (n=xx)						
	V1	**V4**	**V5**	**V7**	**V8**	**V9**	**V10**
B12 Vitamin (pg/)							
N							
Mean							
Median							
Standard Deviation							
Minimum							
Maximum							
Normal							
Abnormal							
CS							
NCS							
Folic acid (ng/mL)							
N							
Mean							
Median							
Standard Deviation							
Minimum							
Maximum							
Normal							
Abnormal							
CS							
NCS							
HbA1c (%)							
N							
Mean							
Median							
Standard Deviation							
Minimum							
Maximum							
Normal							
Abnormal							
CS							
NCS							

CS: Clinically significant; NCS: Not clinically significant.

Table 27 (Cont.) – Biochemistry – Safety population

	Total (n=xx)						
	V1	**V4**	**V5**	**V7**	**V8**	**V9**	**V10**
Fasting blood insulin (µlU/mL))							
N							
Mean							
Median							
Standard Deviation							
Minimum							
Maximum							
Normal							
Abnormal							
CS							
NCS							
Fasting blood glucose (mg/dL)							
N							
Mean							
Median							
Standard Deviation							
Minimum							
Maximum							
Normal							
Abnormal							
CS							
NCS							

CS: Clinically significant; NCS: Not clinically significant.

Table 28 – Tests for liver function – Safety population

	Total (n=xx)						
	V1	**V2**	**V3**	**V4**	**V5**	**V6**	**V10**
SGOT (U/L)							
N							
Mean							
Median							
Standard Deviation							
Minimum							
Maximum							
Normal							
Abnormal							
CS							
NCS							
SGPT (U/L)							
N			-	-	-		
Mean			-	-	-		
Median			-	-	-		
Standard Deviation			-	-	-		
Minimum			-	-	-		
Maximum			-	-	-		
Normal			-	-	-		
Abnormal			-	-	-		
CS			-	-	-		
NCS			-	-	-		
Alkaline Phosphatase (U/L)							
N							
Mean							
Median							
Standard Deviation							
Minimum							
Maximum							
Normal							
Abnormal							
CS							
NCS							

CS: Clinically significant; NCS: Not clinically significant.

Table 28 (Cont.) – Tests for liver function – Safety population

	Total (n=xx)						
	V1	**V2**	**V3**	**V4**	**V5**	**V6**	**V10**
γ-GT (U/L)							
N							
Mean							
Median							
Standard Deviation							
Minimum							
Maximum							
Normal							
Abnormal							
CS							
NCS							
Total bilirubin (mg/dL)							
N							
Mean							
Median							
Standard Deviation							
Minimum							
Maximum							
Normal							
Abnormal							
CS							
NCS							
Direct bilirubin (mg/dL)							
N			-	-	-		
Mean			-	-	-		
Median			-	-	-		
Standard Deviation			-	-	-		
Minimum			-	-	-		
Maximum			-	-	-		
Normal			-	-	-		
Abnormal			-	-	-		
CS			-	-	-		
NCS			-	-	-		

CS: Clinically significant; NCS: Not clinically significant.

Table 28 (Cont.) – Tests for liver function – Safety population

	Total (n=xx)						
	V1	**V2**	**V3**	**V4**	**V5**	**V6**	**V10**
Indirect bilirubin (mg/dL)							
N							
Mean							
Median							
Standard Deviation							
Minimum							
Maximum							
Normal							
Abnormal							
CS							
NCS							
Albumin (g/dL)							
N							
Mean							
Median							
Standard Deviation							
Minimum							
Maximum							
Normal							
Abnormal							
CS							
NCS							

CS: Clinically significant; NCS: Not clinically significant.

Table 29 – Serology – Safety population

	Total (n=xx)
	V1
Hbs-Ag	
N	
Mean	
Median	
Standard Deviation	
Minimum	
Maximum	
Reactive	
Non-reactive	
CS	
NCS	
Anti-HCV	
N	
Mean	
Median	
Standard Deviation	
Minimum	
Maximum	
Reactive	
Non-reactive	
CS	
NCS	

Table 30 – Hormonal evaluation – Safety population

	Total (n=xx)			
	V1	**V4**	**V7**	**V10**
GH (ng/mL)				
N				
Mean				
Median				
Standard Deviation				
Minimum				
Maximum				
Normal				
Abnormal				
CS				
NCS				
IGF-I (ng/mL)				
N				
Mean				
Median				
Standard Deviation				
Minimum				
Maximum				
Normal				
Abnormal				
CS				
NCS				
ACTH (pg/mL)				
N				
Mean				
Median				
Standard Deviation				
Minimum				
Maximum				
Normal				
Abnormal				
CS				
NCS				

CS: Clinically significant; NCS: Not clinically significant.

Table 30 (Cont.) – Hormonal evaluation – Safety population

	Total (n=xx)			
	V1	**V4**	**V7**	**V10**
Cortisol (µg/dl), for patients without intake of glucocorticoid				
N				
Mean				
Median				
Standard Deviation				
Minimum				
Maximum				
Normal				
Abnormal				
CS				
NCS				
LH (mUI/mL)				
N				
Mean				
Median				
Standard Deviation				
Minimum				
Maximum				
Normal				
Abnormal				
CS				
NCS				
FSH (mUI/mL)				
N				
Mean				
Median				
Standard Deviation				
Minimum				
Maximum				
Normal				
Abnormal				
CS				
NCS				

CS: Clinically significant; NCS: Not clinically significant.

Table 30 (Cont.) – Hormonal evaluation – Safety population

	Total (n=xx)			
	V1	**V4**	**V7**	**V10**
Testosterone (ng/dl)				
N				
Mean				
Median				
Standard Deviation				
Minimum				
Maximum				
Normal				
Abnormal				
CS				
NCS				
Estradiol (pg/mL)				
N				
Mean				
Median				
Standard Deviation				
Minimum				
Maximum				
Normal				
Abnormal				
CS				
NCS				
TSH (µUl/mL)				
N				
Mean				
Median				
Standard Deviation				
Minimum				
Maximum				
Normal				
Abnormal				
CS				
NCS				

CS: Clinically significant; NCS: Not clinically significant.

Table 30 (Cont.) – Hormonal evaluation – Safety population

	Total (n=xx)			
	V1	**V4**	**V7**	**V10**
Free T4 (ng/dL)				
N				
Mean				
Median				
Standard Deviation				
Minimum				
Maximum				
Normal				
Abnormal				
CS				
NCS				
Prolactin (ng/mL)				
N				
Mean				
Median				
Standard Deviation				
Minimum				
Maximum				
Normal				
Abnormal				
CS				
NCS				

CS: Clinically significant; NCS: Not clinically significant.

Table 31 – Hormonal evaluation associations – FAS population

	Testosterone replacement therapy	**Without** testosterone replacement therapy	**p-value**
Testosterone (ng/dL) at V1			
N			
Mean			
Median			
Standard Deviation			
Minimum			
Maximum			
	Hormone replacement therapy	**Without Hormone replacement therapy**	
Estradiol (pg/mL) at V1			
N			
Mean			
Median			
Standard Deviation			
Minimum			
Maximum			
	Levothyroxine	**Without Levothyroxine**	**p-value**
TSH (µUl/mL) at V1			
N			
Mean			
Median			
Standard Deviation			
Minimum			
Maximum			
Free T4 (ng/dL) at V1			
N			
Mean			
Median			
Standard Deviation			
Minimum			
Maximum			

Table 32 – Vital signs – Safety population

	Total (n=xx)									
	V1	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Systolic blood pressure (mmHg)										
N										
Mean										
Median										
Standard Deviation										
Minimum										
Maximum										
Diastolic blood pressure (mmHg)										
N										
Mean										
Median										
Standard Deviation										
Minimum										
Maximum										
Heart rate (bpm)										
N										
Mean										
Median										
Standard Deviation										
Minimum										
Maximum										
Temperature (ºC)										
N										
Mean										
Median										
Standard Deviation										
Minimum										
Maximum										

Table 33 – Physical examination – Safety population

	Total (n=xx)									
	V1	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Height (cm)										
N		-	-	-	-	-	-	-	-	-
Mean		-	-	-	-	-	-	-	-	-
Median		-	-	-	-	-	-	-	-	-
Standard Deviation		-	-	-	-	-	-	-	-	-
Minimum		-	-	-	-	-	-	-	-	-
Maximum		-	-	-	-	-	-	-	-	-
Weight (kg)										
N										
Mean										
Median										
Standard Deviation										
Minimum										
Maximum										
Findings, n (%)										
Normal										
Abnormal										
Skin and nails										
Eyes										
Nose and sinuses										
Ears										
Mouth and pharynges										
Head and neck										
Thorax and lungs										
Breast										
Abdomen										
Lymphatic										
Extremities										
Vascular										
Neurological										

Table 34 – Eastern cooperative oncology group performance status – Safety population

	Total (n=xx)									
	V1	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
ECOG result, n (%)										
0										
1										
2										
3										
4										
5										
Total										

ECOG: Eastern Cooperative Oncology Group.

Table 35 – Electrocardiogram – Safety population

	Total (n=xx)									
	V1	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
QTcF (msec)										
N										
Mean										
Median										
Standard Deviation										
Minimum										
Maximum										
Result, n (%)										
Normal										
Abnormal without clinical significance										
Abnormal with clinical significance										
Total										
Consultation with cardiologist to confirm abnormal ECG?, n (%)										
Yes										
No										
Total										
If yes, cardiologist confirm QTcF interval >480msec, n (%)										
Yes										
No										
Total										
Patient discontinued after thorough cardiological examination, n (%)										
Yes										
No										
Total										

Appendix 2: Statistical Tables – Extension study

Table B 1 – Patients' disposition – extension study

	Total (n=xx)
Patient agree to be followed for post-treatment evaluations, n (%)	
Yes	
No	
Total	
Patient agree to be followed for survival, n (%)	
Yes	
No	
Total	
Primary reason for end of treatment, n (%)	
Adverse Event(s)	
Subject withdrew consent	
Lost to follow-up	
Administrative problems.	
Death	
Disease progression	
Subject is unable to tolerate the minimum pasireotide LAR dose of 40 mg.	
Acute or progressive vision loss confirmed by a new visual field evaluation.	
Pregnancy	
Uncontrolled diabetes mellitus.	
Clinically significant abnormal test procedure result(s).	
Clinically significant abnormal laboratory value(s)	
Protocol deviation	
Investigator's decision	
Other	
Study populations, n (%)	
FAS	
Safety	

Table B 2 – Concomitant medication – extension study – FAS population

	Total (n=xx)
Any medication or significant non-drug therapy, n (%)	
Yes	
No	
Total	

Table B 3 – Treatment – extension study – FAS population

	Total (n=xx)					
	V13	**V16**	**V19**	**V22**	**V25**	**Extension phase**
Study medication administered, n (%)						
Yes						-
No						-
Total						-
Dose, n (%)						
60 mg						-
40 mg						-
Total						-
Exposure (days)[a)]						
N						
Mean						
Median						
Standard Deviation						
Minimum						
Maximum						
Mean administration dose (mg)[b)]						
N						
Mean						
Median						
Standard Deviation						
Minimum						
Maximum						

a) The difference between the last administration and the first administration of extension phase, in days.
b) Cumulative dose (total dose administered in the extension phase) divided by number administrations (extension phase).

Table B 4 – Magnetic resonance imaging – FAS population

	Total (n=xx)		
	V16	**V22**	**V28**
Volume (cm^3)			
N			-
Mean			-
Median			-
Standard Deviation			
Minimum			
Maximum			-
Tumor is not visible			-
Missing values			-
Volume change[a] (cm^3)			
N			
Mean			
Median			
Standard Deviation			
Minimum			
Maximum			
Percentage change in volume[a] (%)			
N			
Mean			
Median			
Standard Deviation			
Minimum			
Maximum			
Reduction of tumor volume[b], n (%)			
Yes			
No			
≥20% tumor volume reduction[c], n (%)			
Yes			
No			
Total			
≥20% tumor volume reduction using LOCF method, n (%)			
Yes			
No			
Total			
For patients who achieved a reduction in tumor volume of at least 20% with respect to the initial tumor volume in the core phase			
≥20% tumor volume reduction[c], n (%)			
Yes			
No			
Total			
For patients who achieved a reduction in tumor volume < 20% with respect to the initial tumor volume in the core phase			
≥20% tumor volume reduction[c], n (%)			
Yes			
No			
Total			

a) The difference between visit i and V1.
b) For reduction='yes' will be considered all patients who obtained 'volume in visit i – volume in V1' >0.
c) For reduction ≥20%='yes' will be considered all patients who obtained 'Percentage change in volume at visit i' ≥20.

Table B 5 – Disease-related symptoms – FAS population

	Total (n=xx)					
	V13	**V16**	**V19**	**V22**	**V25**	**V28**
Headache, n (%)						
Absent						
Mild						
Moderate						
Severe						
Very severe						
Total						
Improved, n (%)						
Yes						
No						
Total						
Visual disturbances, n (%)						
Absent						
Mild						
Moderate						
Severe						
Very severe						
Total						
Improved, n (%)						
Yes						
No						
Total						
Fatigue, n (%)						
Absent						
Mild						
Moderate						
Severe						
Very severe						
Total						
Improved, n (%)						
Yes						
No						
Total						
Erectile dysfunction, n (%)						
Yes						
No						
Total						
Improved, n (%)						
Yes						
No						
Total						
Regular menses, n (%)						
Yes						
No						
Total						
Improved, n (%)						
Yes						
No						
Total						

a) For each symptom, it will considered as improvement if the severity reduce at least one point (eg. 'Severe' at v_1 and 'moderate' at v_i will be considered as improvement in vi).
b) For patients who registered 'No' in V_1 and 'Yes' in v_i it will be considered as an improvement in v_i.
c) For patients who registered 'No' in V_1 and 'Yes' in v_i it will be considered as an improvement in v_i.

Table B 6 – [redacted] Alpha-subunit – FAS population

	Total (n=xx)		
	V16	**V22**	**V28**
[redacted]			
α subunit (ng/mL)			
N		-	
Mean		-	
Median		-	
Standard Deviation		-	
Minimum		-	
Maximum		-	
Normal		-	
Abnormal		-	
CS		-	
NCS		-	
Reduction of α subunit ≥50%[b], n (%)			
Yes		-	
No		-	
Total		-	

CS: Clinically significant; NCS: Not clinically significant.

[redacted]

b) For reduction ≥50%='yes' will be considered all patients who obtained percentage change from baseline in α subunit at visit i' ≥50.

Table B 7 – Visual field – FAS population

	Total (n=xx)		
	V16	**V22**	**V28**
Right eye			
Normal/abnormal, n (%)			
Normal			
Abnormal			
Mild			
Severe			
Total			
Findings, n (%)			
Upper right quadrantanopia			
Upper left quadrantanopia			
Lower right quadrantanopia			
Lower left quadrantanopia			
Temporal hemianopsia			
Nasal hemianopsia			
Other			
Evolutive information, n (%)			
Stable			
Improved			
Worsened			
Total			
Left eye			
Normal/abnormal, n (%)			
Normal			
Abnormal			
Mild			
Severe			
Total			
Findings, n (%)			
Upper right quadrantanopia			
Upper left quadrantanopia			
Lower right quadrantanopia			
Lower left quadrantanopia			
Temporal hemianopsia			
Nasal hemianopsia			
Other			
Evolutive information, n (%)			
Stable			
Improved			
Worsened			
Total			

Table B 8 – Gallblader ultrasound – FAS population

	Total (n=xx)	
	V16	**V28**
Gallblader ultrasound performed, n (%)		
Yes		
No		
Total		
If yes		
Any gallstones detected, n (%)		
Yes		
No		
Total		
Any sludge detected, n (%)		
Yes		
No		
Total		
Dilatation of the intra or extra hepatic ductal system, n (%)		
Yes		
No		
Total		
Location of dilatation, n (%)		
Intrahepatic ductal system		
Extrahepatic ductal system		
Total		

Table B 9 – Adverse events and serious adverse events in the extension study – Safety population

	Total (n=xx)
Patients with at least one adverse event, n (%)[a)]	
No	
Yes	
Total	
Patients with at least one serious adverse event, n (%)[a)]	
Yes	
No	
Total	
Grade of adverse events, n (%)[b)]	
Grade 1	
Grade 2	
Grade 3	
Grade 4	
Total	
Grade ≥ 3	
Relationship of study drug, n (%)[b)]	
Not suspected	
Suspected	
Total	
Action taken for adverse event, n (%)[b)]	
No action taken.	
Study drug dosage adjusted / temporarily interrupted.	
Study drug permanently discontinued due to this adverse event	
Concomitant medication taken	
Non-drug therapy given	
Hospitalization / prolonged hospitalization	
Serious adverse events, n (%)[b)]	
Yes	
No	

a) Percentage calculated within the total number of patients of safety population (n=xx).
b) Percentage calculated within the total number of adverse events reported by safety population (n=xxx).

Table B 10 – Incidence of adverse events in the extension study – Safety population

	Total (n=xx)
Incidence of adverse events, n (%)	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	

a) Percentage calculated for total of patients of patients of the safety population (n=xx).

Table B 11 – Incidence of serious adverse events in the extension study – Safety population

	Total (n=xx)
Incidence of serious adverse events, n (%)	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	

a) Percentage calculated for total of patients of patients of the safety population (n=xx).

Table B 12 – Incidence of serious adverse events with suspected relationship with study drug in the extension study – Safety population

	Total (n=xx)
Incidence of adverse events with suspected relationship with study drug, n (%)	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	

a) Percentage calculated for total of patients of patients of the safety population (n=xx).

Table B 13 – Incidence of serious adverse events with suspected relationship with study drug in the extension study – Safety population

	Total (n=xx)
Incidence of serious adverse events with suspected relationship with study drug, n (%)	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	

a) Percentage calculated for total of patients of patients of the safety population (n=xx).

Table B 14 – Adverse events in the extension study – Safety population

	Total (n=xx)
Adverse events, n (%)	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	

Percentage calculated within the total number of adverse events reported by safety population (n=xxxx).

Table B 15 – Serious adverse events in the extension study – Safety population

	Total (n=xx)
Serious adverse events, n (%)	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	

Percentage calculated within the total number of serious adverse events reported by safety population (n=xxxx).

Table B 16 – Adverse events with suspected relationship with study drug in the extension study – Safety population

	Total (n=xx)
Adverse events with suspected relationship with study drug, n (%)	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	

Percentage calculated within the total number of adverse events with remote, possible or probable relationship with study drug reported by safety population (n=xxxx).

Table B 17 – Serious adverse events with suspected relationship with study drug in the extension study – Safety population

	Total (n=xx)
Serious adverse events with suspected relationship with study drug, n (%)	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	
Xxxxx	

Percentage calculated within the total number of serious adverse events with remote, possible or probable relationship with study drug reported by safety population (n=xxxx).

Table B 18 – Hematology – Safety population

	Total (n=xx)		
	V16	**V22**	**V28**
RBC count ((million/mm³)			
N			
Mean			
Median			
Standard Deviation			
Minimum			
Maximum			
Normal			
Abnormal			
CS			
NCS			
Hemoglobin (g/dL)			
N			
Mean			
Median			
Standard Deviation			
Minimum			
Maximum			
Normal			
Abnormal			
CS			
NCS			
Hematocrit (%)			
N			
Mean			
Median			
Standard Deviation			
Minimum			
Maximum			
Normal			
Abnormal			
CS			
NCS			
RBC count ((million/mm³)			
N			
Mean			
Median			
Standard Deviation			
Minimum			
Maximum			
Normal			
Abnormal			
CS			
NCS			
Hemoglobin (g/dL)			
N			
Mean			
Median			
Standard Deviation			
Minimum			
Maximum			
Normal			
Abnormal			
CS			
NCS			

Hematocrit (%)
- N
- Mean
- Median
- Standard Deviation
- Minimum
- Maximum

- Normal
- Abnormal
  - CS
  - NCS

WBC count (/mm³)
- N
- Mean
- Median
- Standard Deviation
- Minimum
- Maximum

- Normal
- Abnormal
  - CS
  - NCS

Eosinophils (/mm³)
- N
- Mean
- Median
- Standard Deviation
- Minimum
- Maximum

- Normal
- Abnormal
  - CS
  - NCS

Neutrophils total (/mm³)
- N
- Mean
- Median
- Standard Deviation
- Minimum
- Maximum

- Normal
- Abnormal
  - CS
  - NCS

Lymphocytes (/mm³)
- N
- Mean
- Median
- Standard Deviation
- Minimum
- Maximum

- Normal
- Abnormal
  - CS
  - NCS

Monocytes (/mm³)
- N
- Mean
- Median

Standard Deviation
Minimum
Maximum

Normal
Abnormal
CS
NCS

Basophils (/mm³)
N
Mean
Median
Standard Deviation
Minimum
Maximum

Normal
Abnormal
CS
NCS

Band neutrophils (/mm³)
N
Mean
Median
Standard Deviation
Minimum
Maximum

Normal
Abnormal
CS
NCS

Platelet count (thousand/mm³)
N
Mean
Median
Standard Deviation
Minimum
Maximum

Normal
Abnormal
CS
NCS

CS: Clinically significant; NCS: Not clinically significant.

Table B 19 – Coagulation – Safety population

	Total (n=xx)						
	V13	**V16**	**V19**	**V22**	**V25**	**V28**	**V29**
PT (%)							
N							
Mean							
Median							
Standard Deviation							
Minimum							
Maximum							
Normal							
Abnormal							
CS							
NCS							
Total							
APTT (%)							
N							
Mean							
Median							
Standard Deviation							
Minimum							
Maximum							
Normal							
Abnormal							
CS							
NCS							
Total							

Table B 20 – Urinalysis – Safety population

	Total (n=xx)		
	V16	**V22**	**V28**
Specific gravity			
N			
Mean			
Median			
Standard Deviation			
Minimum			
Maximum			
Normal			
Abnormal			
CS			
NCS			
PH			
N			
Mean			
Median			
Standard Deviation			
Minimum			
Maximum			
Normal			
Abnormal			
CS			
NCS			
Glucose, n (%)			
Negative			
100 mg/dl or 5 mmol/L			
250 (+)mg/dl or 15 mmol/L			
500 (++)mg/dl or 30 mmol/L			
1000 (+++)mg/dl or 60 mmol/L			
2000 (++++) mg/dL or 110 mmol/L			
Total			
Normal			
Abnormal			
CS			
NCS			
Protein, n (%)			
Negative			
Trace			
30 (+)mg/dl or 0.3 g/L			
100 (++)mg/dl or 1.0 g/L			
300 (+++)mg/dl or 3.0 g/L			
> 2000 (++++) mg/dL or > 20 g/L			
Total			
Normal			
Abnormal			
CS			
NCS			
Blood, n (%)			
Negative or 0 ca Cells/µL			
“Non – Hemolyzed” or 10 ca Cells/µL (Trace)			
“Hemolyzed” or “ Trace”			
“ Small” (+) or 25 ca Cells/µL			
“Moderate” (++) or 80 ca Cells/µL			
“Large“ (+++) or 200 ca Cells/µL			
Total			
Normal			

Abnormal
CS
NCS

Bilirubin, n (%)
Negative
"Small " (+)
"Moderate" (++)
"Large" (+++)
Total
Not applicable

Normal
Abnormal
CS
NCS

Ketones, n (%)
"Negative"
"Trace" (5 mg/dl) or 0.5 mmol/L
"Small" (15 mg/dl) or 1.5 mmol/L
"Moderate" (40 mg/dl) or 4.0 mmol/L
"Large" (80 mg/dl) or 8.0 mmol/L
"Large" (160 mg/dl) or 16 mmol/L
Total

Normal
Abnormal
CS
NCS

Leukocytes, n (%)
Negative or 0 ca Cells/µL
"Trace" or 15 ca Cells/µL
" Small" (+) or 70 ca Cells/µL
"Moderate" (++) or 125 ca Cells/µL
"Large" (+++) or 500 ca Cells/µL
Total
Not applicable

Normal
Abnormal
CS
NCS

CS: Clinically significant; NCS: Not clinically significant.

Table B 21 – Biochemistry – Safety population

	Total (n=xx)		
	V16	**V22**	**V28**
Urea (mg/dL)			
N			
Mean			
Median			
Standard Deviation			
Minimum			
Maximum			
Normal			
Abnormal			
CS			
NCS			
Creatinine (mg/dL)			
N			
Mean			
Median			
Standard Deviation			
Minimum			
Maximum			
Normal			
Abnormal			
CS			
NCS			
Uric acid (mg/dL)			
N			
Mean			
Median			
Standard Deviation			
Minimum			
Maximum			
Normal			
Abnormal			
CS			
NCS			
CPK (U/L)			
N			
Mean			
Median			
Standard Deviation			
Minimum			
Maximum			
Normal			
Abnormal			
CS			
NCS			
LDH (U/L)			
N			
Mean			
Median			
Standard Deviation			
Minimum			
Maximum			
Normal			
Abnormal			
CS			
NCS			

Total protein (mg/dL)
N
Mean
Median
Standard Deviation
Minimum
Maximum

Normal
Abnormal
CS
NCS

Total cholesterol (mg/dL)
N
Mean
Median
Standard Deviation
Minimum
Maximum

Normal
Abnormal
CS
NCS

Low density lipoprotein (LDL) cholesterol (mg/dL)
N
Mean
Median
Standard Deviation
Minimum
Maximum

Normal
Abnormal
CS
NCS

High-density lipoprotein (HDL) cholesterol (mg/dL)
N
Mean
Median
Standard Deviation
Minimum
Maximum

Normal
Abnormal
CS
NCS

Triglycerides (mg/dL)
N
Mean
Median
Standard Deviation
Minimum
Maximum

Normal
Abnormal
CS
NCS

Sodium (mEq/L)
N
Mean
Median

Standard Deviation
Minimum
Maximum

Normal
Abnormal
CS
NCS

Potassium (mEq/L)
N
Mean
Median
Standard Deviation
Minimum
Maximum

Normal
Abnormal
CS
NCS

Calcium (mg/dL)
N
Mean
Median
Standard Deviation
Minimum
Maximum

Normal
Abnormal
CS
NCS

Phosphorus (mg/dL)
N
Mean
Median
Standard Deviation
Minimum
Maximum

Normal
Abnormal
CS
NCS

Chloride (mEq/L)
N
Mean
Median
Standard Deviation
Minimum
Maximum

Normal
Abnormal
CS
NCS

B12 Vitamin (pg/)
N
Mean
Median
Standard Deviation
Minimum
Maximum

Normal

Abnormal
CS
NCS

Folic acid (ng/mL)
N
Mean
Median
Standard Deviation
Minimum
Maximum

Normal
Abnormal
CS
NCS

HbA1c (%)
N
Mean
Median
Standard Deviation
Minimum
Maximum

Normal
Abnormal
CS
NCS

Fasting blood insulin (µlU/mL))
N
Mean
Median
Standard Deviation
Minimum
Maximum

Normal
Abnormal
CS
NCS

Fasting blood glucose (mg/dL)
N
Mean
Median
Standard Deviation
Minimum
Maximum

Normal
Abnormal
CS
NCS

CS: Clinically significant; NCS: Not clinically significant.

Table B 22 – Tests for liver function – Safety population

	Total (n=xx)		
	V16	**V22**	**V28**
SGOT (U/L)			
N			
Mean			
Median			
Standard Deviation			
Minimum			
Maximum			
Normal			
Abnormal			
CS			
NCS			
SGPT (U/L)			
N			
Mean			
Median			
Standard Deviation			
Minimum			
Maximum			
Normal			
Abnormal			
CS			
NCS			
Alkaline Phosphatase (U/L)			
N			
Mean			
Median			
Standard Deviation			
Minimum			
Maximum			
Normal			
Abnormal			
CS			
NCS			
y-GT (U/L)			
N			
Mean			
Median			
Standard Deviation			
Minimum			
Maximum			
Normal			
Abnormal			
CS			
NCS			
Total bilirubin (mg/dL)			
N			
Mean			
Median			
Standard Deviation			
Minimum			
Maximum			
Normal			
Abnormal			
CS			
NCS			

Direct bilirubin (mg/dL)
N
Mean
Median
Standard Deviation
Minimum
Maximum

Normal
Abnormal
CS
NCS

Indirect bilirubin (mg/dL)
N
Mean
Median
Standard Deviation
Minimum
Maximum

Normal
Abnormal
CS
NCS

Albumin (g/dL)
N
Mean
Median
Standard Deviation
Minimum
Maximum

Normal
Abnormal
CS
NCS

CS: Clinically significant; NCS: Not clinically significant.

Table B 23 – Hormonal evaluation – Safety population

	Total (n=xx)		
	V16	**V22**	**V28**
GH (ng/mL)			
N			
Mean			
Median			
Standard Deviation			
Minimum			
Maximum			
Normal			
Abnormal			
CS			
NCS			
IGF-I (ng/mL)			
N			
Mean			
Median			
Standard Deviation			
Minimum			
Maximum			
Normal			
Abnormal			
CS			
NCS			
ACTH (pg/mL)			
N			
Mean			
Median			
Standard Deviation			
Minimum			
Maximum			
Normal			
Abnormal			
CS			
NCS			
Cortisol (µg/dl), for patients without intake of glucocorticoid			
N			
Mean			
Median			
Standard Deviation			
Minimum			
Maximum			
Normal			
Abnormal			
CS			
NCS			
LH (mUI/mL)			
N			
Mean			
Median			
Standard Deviation			
Minimum			
Maximum			
Normal			
Abnormal			
CS			
NCS			

FSH (mUI/mL)
N
Mean
Median
Standard Deviation
Minimum
Maximum

Normal
Abnormal
CS
NCS

Testosterone (ng/dl)
N
Mean
Median
Standard Deviation
Minimum
Maximum

Normal
Abnormal
CS
NCS

Estradiol (pg/mL)
N
Mean
Median
Standard Deviation
Minimum
Maximum

Normal
Abnormal
CS
NCS

TSH (µUI/mL)
N
Mean
Median
Standard Deviation
Minimum
Maximum

Normal
Abnormal
CS
NCS

Free T4 (ng/dL)
N
Mean
Median
Standard Deviation
Minimum
Maximum

Normal
Abnormal
CS
NCS

Prolactin (ng/mL)
N
Mean
Median

Standard Deviation Minimum Maximum Normal Abnormal CS NCS

CS: Clinically significant; NCS: Not clinically significant.

Table B 24 – Vital signs – Safety population

	Total (n=xx)						
	V13	**V16**	**V19**	**V22**	**V25**	**V28**	**V29**
Systolic blood pressure (mmHg)							
N							
Mean							
Median							
Standard Deviation							
Minimum							
Maximum							
Diastolic blood pressure (mmHg)							
N							
Mean							
Median							
Standard Deviation							
Minimum							
Maximum							
Heart rate (bpm)							
N							
Mean							
Median							
Standard Deviation							
Minimum							
Maximum							
Temperature (ºC)							
N							
Mean							
Median							
Standard Deviation							
Minimum							
Maximum							

Table B 25 – Physical examination – Safety population

	Total (n=xx)						
	V13	**V16**	**V19**	**V22**	**V25**	**V28**	**V29**
Weight (kg)							
N							
Mean							
Median							
Standard Deviation							
Minimum							
Maximum							
Findings, n (%)							
Normal							
Abnormal							
Skin and nails							
Eyes							
Nose and sinuses							
Ears							
Mouth and pharynges							
Head and neck							
Thorax and lungs							
Breast							
Abdomen							
Lymphatic							
Extremities							
Vascular							
Neurological							

Table B 26 – Eastern cooperative oncology group performance status – Safety population

	Total (n=xx)						
	V13	**V16**	**V19**	**V22**	**V25**	**V28**	**V29**
ECOG result, n (%)							
0							
1							
2							
3							
4							
5							
Total							

ECOG: Eastern Cooperative Oncology Group.

Table B 27 – Electrocardiogram – Safety population

	Total (n=xx)					
	V13	**V16**	**V19**	**V22**	**V25**	**V28**
QTcF (msec)						
N						
Mean						
Median						
Standard Deviation						
Minimum						
Maximum						
Result, n (%)						
Normal						
Abnormal without clinical						
Abnormal with clinical						
Total						
Consultation with cardiologist to confirm abnormal ECG?, n (%)						
Yes						
No						
Total						
If yes, cardiologist confirm QTcF interval >480msec, n (%)						
Yes						
No						
Total						
Patient discontinued after thorough cardiological examination, n (%)						
Yes						
No						
Total						