Pasireotide LAR® Depot

Protocol No. CSOM230GUS44T

PILOT STUDY OF PASIREOTIDE LAR TREATMENT OF SILENT CORTICOTROPH PITUITARY TUMORS AND EFFECTS ON PLASMA LEVELS OF POMC

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Compound name: Pasireotide LAR® Depot

Protocol number: CSOM230GUS44T

I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

Pamela U. Freda MD
(Principal Investigator) _____ Signature _____ date

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PROTOCOL SUMMARY

Protocol number: CSOM230GUS44T

Title PILOT STUDY OF PASIREOTIDE LAR TREATMENT OF SILENT CORTICOTROPH PITUITARY TUMORS AND EFFECTS ON PLASMA LEVELS OF POMC

Clinical Phase: Phase II

Investigation Type: Drug

Study Type: Interventional

Purpose and Rationale: The purpose of this trial is to test the main hypotheses that Pasireotide LAR treatment of patients with silent corticotroph pituitary tumors and elevated or normal plasma POMC levels will reduce plasma POMC levels and this will be associated with a reduction in pituitary tumor size.

Primary Objective: To determine the efficacy of Pasireotide LAR to suppress plasma levels of POMC in patients with silent corticotroph pituitary tumors.

Secondary Objectives: To determine the effect of Pasireotide LAR therapy on pituitary tumor volume in patients with silent corticotroph pituitary tumors.

Study design: This is an open-label, 12-month pilot study of Pasireotide LAR therapy of 10 patients with silent corticotroph pituitary tumors. Pasireotide LAR 40 mg will be administered monthly. Baseline and monthly visits on therapy will monitor plasma levels of POMC, other pituitary function, safety labs, glucose tolerance, physical examination, and visual fields. Pituitary MRI will be done at baseline, 6 months and 12 months of therapy. The starting dose is Pasireotide LAR 40 mg/month given as intramuscular injection. The dose will be increased to 60 mg/month at 6 months if a fall in POMC levels and/or tumor shrinkage are not attained. LAR will be administered monthly with the last injection at Week 44.

Study Population: The eligible patient population will consist of adult patients with known silent corticotroph pituitary tumors and elevated or normal plasma levels of POMC.

Key Inclusion criteria:

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

- Adults (males and females, ages 18-70 years) with a diagnosis of a clinically nonfunctioning pituitary tumor of the silent corticotroph tumor type (i.e. positive ACTH staining on immunohistochemical staining of the pituitary tumor obtained at surgery)
- Plasma POMC level within or greater than the upper limit of normal

- Prior pituitary tumor surgery with residual or recurrent pituitary tumor visible on MRI scan that is ≥ 5 mm from the optic chiasm
- Surgical resection of the pituitary adenoma must have occurred two or more months prior to the baseline visit.
- If patients have undergone pituitary radiotherapy they must have completed their course of radiotherapy at least 2 months prior to study screening
- No prior somatostatin analog therapy
- No concurrent use of dopamine agonist therapy
- No active malignancy
- Stable pituitary hormone supplements (x 2 months) prior to baseline visit
- Sign and date an informed consent document indicating that the subject has been informed of and agrees to all pertinent aspects of the trial

Key Exclusion criteria
• Patients with Cushing's disease (biochemical evidence of hypercortisolism)
• Patients who require surgical intervention.
• HbA1c > 8 % at screening
• Known hypersensitivity to somatostatin analogues
• History of liver disease
• Symptomatic cholelithiasis or acute or chronic pancreatitis
• Cardiac or repolarization abnormality
• Life-threatening autoimmune disorders
• Inadequately treated adrenal or thyroid insufficiencies
• Inadequate bone marrow function

Investigational therapy: Pasireotide LAR

Efficacy assessments
Primary efficacy parameter: Change in plasma POMC levels from baseline to 12 months of Pasireotide LAR treatment.

Secondary efficacy parameter: Change in pituitary tumor volume from baseline to 12 months of Pasireotide LAR treatment.

Safety assessments
- Adverse Events
- Laboratory evaluations
- Cardiac assessments (ECG)
- Vital Signs
- Blood glucose monitoring
- Gall bladder ultrasound
- Pituitary MRI

1 BACKGROUND

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Silent Corticotroph Pituitary Adenomas

Clinically non-functioning pituitary adenomas (CNFAs), the subtype of pituitary adenomas that does not appear to secrete biologically active hormone nor to have a characteristic clinical phenotype, are the most common type of pituitary macroadenoma at diagnosis. Many CNFAs are of gonadotroph cell origin (1), but some CNFAs are of corticotroph cell origin (2) These "silent" corticotroph adenomas show adrenocorticotropic hormone (ACTH) by immunohistochemistry, but do not secrete biologically active ACTH and thus do not have biochemical evidence of cortisol excess or produce a clinical syndrome of glucocorticoid excess (3). Although typically categorized as a type of nonfunctioning pituitary tumor, such silent corticotroph adenomas seem to be at one end of the spectrum of the ACTH producing pituitary tumors that produce clinical Cushing's disease (CD). Some data suggest that the cell of origin of the silent corticotroph tumor cell is a corticotroph progenitor cell (4). Other data also suggest that there may be dysfunctional processing of pituitary hormones within the cells of silent corticotroph tumors (5-7). This is supported by the findings that increased amounts of mRNA of the ACTH precursor POMC have been measured in silent corticotroph tumors (8-10). ACTH derives from a pro-opiomelanocortin (POMC) precursor, that is cleaved at the C-terminal of ACTH by prohormone convertase (PC) 1, to give rise to β - LPH and pro-ACTH. β-LPH and pro-ACTH are further cleaved into N-terminal POMC, joining peptide (JP) and ACTH, prior to additional processing by PC2 and post-translational modification. The extent of POMC processing varies from tissue to tissue, and in ACTH dependent Cushing's syndrome, POMC processing appears to depend on the degree of tumor cell differentiation. Data from early chromatographic studies suggests that ectopic ACTH-producing tumors secrete high molecular weight ACTH precursors. Other data, including a recent study conducted by our co-investigator, Dr. Page-Wilson, have found that patients with ectopic ACTH tumors have higher levels of ACTH precursors, reflecting decreased POMC processing, than patients with Cushing's disease (11-14). Elevations of POMC precursors have been found in some patients with silent corticotroph adenomas (15-17), consistent with the less differentiated state of the tumor cells.

There is currently no option for medical therapy of CNFA, in general, or specifically of silent corticotroph tumors. Silent corticotroph tumors can range from being completely asymptomatic to becoming large and causing significant hypothalamic/pituitary dysfunction and visual symptoms, and most data support that this type of tumor has a more aggressive phenotype (10,18,19). Current therapy consists primarily of surgical removal of the tumor and for recurrent or residual tumors, repeated surgery and/or radiotherapy. In very aggressive tumors, chemotherapy has been tried with some success (20). Therefore, a need exists for a medical therapeutic option for the treatment of this tumor type. This project assesses this clinical need.

This protocol is a pilot study of the efficacy of Pasireotide LAR for the treatment of silent corticotroph pituitary tumors that have elevated plasma levels of POMC. We hypothesize that elevated plasma POMC levels will be a marker for this tumor type and the response of this tumor type to Pasireotide LAR therapy.

1.2 Introduction to Investigational Treatment

Somatostatin is an endogenous peptide that modulates a number of exocrine and endocrine secretions. Pasireotide is a somatostatin analog (SSA) with a broader somatostatin receptor binding profile relative to currently available somatostatin analogs (e.g., octreotide, SMS 201-995, Sandostatin®). Pasiretodie LAR (Brand name SIGNIFOR LAR) is a somatostatin analog indicated for the treatment of patients with acromegaly who have had an inadequate response to surgery and/or for whom surgery is not an option. Pasireotide LAR (SIGNIFOR® LAR) is a long acting release injectable suspension for intramuscular use. It was approved in the U.S. in 2012 for the treatment of acromegaly. Pasireotide is also available in a short acting subcutaneously administered from which is approved for the treatment of Cushing's disease. As of the cut-off date of April 24, 2015, Pasireotide (Brand name Signifor®) as subcutaneous formulation has been granted marketing authorization in more than 75 countries and pasireotide as long-acting depot formulation in more than 30 countries worldwide. Pasireotide LAR is also being studied for the treatment of patients with Cushing's disease, neuroendocrine tumors (NET), and dumping syndrome.

1.2.1 Overview of Pasireotide (SOM230)

Pasireotide (SOM230) is a cyclohexapeptide SSA with the following chemical name: (2Aminoethyl)carbamic acid (2R,5S,8S,11S,14R,17S,19aS)-11-(4-aminobutyl)-5-benzyl-8-(4-benzyloxybenzyl)-14-(1H-indol-3ylmethyl)-4,7,10,13,16,19-hexaoxo-17-phenyloctadecahydro-3a,6,9,12,15,18-hexaazacyclopentacyclooctadeen-2-yl ester, di[(S)-2aminosuccinic acid] salt. Like natural somatostatin and other SSAs, pasireotide exerts its pharmacological activity via binding to somatostatin receptors (sst). Somatostatin is an endogenous peptide that modulates a number of exocrine and endocrine secretions. There are five known somatostatin receptors: sst1, 2, 3, 4 and 5. When compared to octreotide, pasireotide has a binding affinity, which is 30-40 times greater for sst1and sst5, 5 times greater for sst3, and a comparable affinity for sst2 (21,22). Somatostatin receptors are expressed in different tissues under normal physiological conditions as well as in many solid tumors, especially in neuroendocrine tumors where hormones are excessively secreted, e.g. acromegaly, gastroenteropancreatic neuroendocrine tumor (GEP/NET) and Cushing's disease (22-26). A detailed summary of available preclinical data is provided in the Investigator's Brochure (attached).

1.2.1.1 Clinical Experience

1.2.1.1.1 Pasireotide LAR

Pasireotide LAR has been extensively investigated in the clinical development program for healthy volunteers and various patient populations. Completed studies and studies with completed interim analyses are shown in the INVESTIGATOR'S BROCHURE, V15, P. 44, Table 5-1.

Pasireotide LAR demonstrated favorable PK profile for extended release in healthy volunteers and patients. PK steady state was achieved following 3 monthly (q28d) intra-muscular (i.m.) injections of pasireotide LAR in a study with both acromegaly and carcinoid patients. PK exposures of trough concentrations were approximately dose-proportional. CL/F of the Pasireotide LAR formulation was comparable to CL/F of the s.c. formulation (4.3-9.0 L/h). T1/2 for the Pasireotide LAR formulation was approximately 16 days, suitable for monthly dosing. The relative bioavailability of the Pasireotide LAR formulation to the s.c. formulation was complete, ranging from 106% to 148%. PK exposures in acromegaly patients were comparable to those in healthy volunteers. PK exposures in carcinoid patients were 2-fold higher than in healthy volunteers.

The efficacy of pasireotide LAR in acromegaly patients is based on CSOM230C2305, the phase III study to assess the safety and efficacy of pasireotide LAR vs octreotide LAR in patients with active acromegaly. In this study, pasireotide LAR was shown to be significantly superior to octreotide LAR for the treatment of acromegaly in medically naïve patients in terms of biochemical control (GH < 2.5 µg/L and normalization of IGF-1 levels) (31.3% vs. 19.2%; p-value 0.007), providing higher response rate in both de novo patients and in patients with prior pituitary surgery (25.7% vs. 17.3% in de novo patients; 39.4% vs. 21.8% in postsurgical patients). Pasireotide LAR was as effective as octreotide LAR in reducing tumor volume, improving acromegaly symptoms and ring size, and quality of life (27).

Safety and efficacy in humans is summarized in the Investigator's Brochure, version 15, section 5.2. Pasireotide LAR safety is based on studies in patients with Acromegaly, Investigator's Brochure, V15, section 5.2.1.1.3. Safety assessment was based on 491 acromegaly patients who received pasireotide (419 patients received pasireotide LAR and 72 received pasireotide s.c.) in Phase I, II and III studies. The safety profile of pasireotide LAR is consistent with the somatostatin analogs class, except for the higher degree and frequency of hyperglycemia seen with pasireotide LAR. In Study SOM230C2305, the mean duration of exposure to pasireotide LAR across core and extension phase was 75 weeks (N=178).

The most frequent ADRs reported for more than 15% in the pasireotide LAR or octreotide LAR arms core and extension phase were diarrhea (33.1% and 40.6%), cholelithiasis (30.9% and 36.7%), hyperglycemia (28.1% and 7.2%) and diabetes mellitus (19.7% and 3.9%), alopecia (15.7% and 14.4%) and abdominal pain (12.9% and 17.8). Common Toxicity Criteria (CTC) grade 3 or 4 ADRs reported for more than 2% of the patients in the pasireotide LAR and octreotide LAR arms were diabetes mellitus (4.5% and 0%), diarrhea (0.6% and 2.8%) and hyperglycemia (2.2% and 0.6%). ADRs reported in patients who crossed over to the other treatment arm in the Phase III study were similar to those reported in the core and extension.

In the Phase III Study SOM230C2402, The mean duration of exposure in the core phase of Study C2402 was 24 weeks for all treatment groups.

The most frequent ADRs observed for more than 10% in pasireotide LAR 40 mg, 60 mg or active control in the 24-week core phase of study SOM230C2402 were hyperglycemia (33.3%, 29.0% and 6.1%), diabetes mellitus (19.0%, 25.8% and 4.5%) and diarrhea (11.1%, 19.4 and 1.5%), and cholelithiasis (9.5%, 11.3% and 12.1%). CTC grade 3 or 4 ADRs reported for more than 2% of the patients in pasireotide LAR 40 mg, 60 mg and active control were hyperglycemia (11.1%, 8.1% and 0%), and diabetes mellitus (0%, 3.2% and 0%). Adverse drug reactions for Phase III study SOM230C2305 core and extension phase in medically naïve and Phase III study SOM230C2402 in inadequately controlled acromegaly patients with frequency of at least 5% in any pasireotide LAR treatment arm of either study and other notable ADRs which occurred in the two Phase III studies with a frequency of equal or less than 5% are: anemia, adrenal insufficiency, hyperglycemia, diabetes mellitus, type II diabetes mellitus, impaired glucose tolerance, dizziness, headache, diarrhea, sinus bradycardia, QT prolongation, abdominal pain, abdominal distention, nausea, cholelithiasis, alopecia, injection site reaction, increased blood creatine phosphokinase, increased blood glucose, increased alanine aminotransferase, increased glycosylated hemoglobin, and increased blood amylase (27).

2 RATIONALE

2.1 Study Rationale and Purpose

There is currently no option for medical therapy of CNFA, in general, or specifically of silent corticotroph tumors. Silent corticotroph tumors can range from being completely asymptomatic to becoming large and causing significant hypothalamic/pituitary dysfunction and visual symptoms, and most data support that this type of tumor has a more aggressive phenotype (10,18,19). Current therapy consists primarily of surgical removal of the tumor and for recurrent or residual tumors, repeated surgery and/or radiotherapy. In very aggressive tumors, chemotherapy has been tried with some success (20). Therefore, a need exists for a medical therapeutic option for the treatment of this tumor type.

Corticotroph cell tumors rarely respond to the somatostatin analogs octreotide or lanreotide. However, some data suggest that the multi-receptor somatostatin analog Pasireotide, which is effective for Cushing's disease, may be effective for some silent corticotroph tumors. Analyses of the somatostatin receptor profile of silent corticotroph tumors suggests that the receptor profile of silent corticotroph tumor cells would confer a more favorable response of this tumor type to pasireotide. In two studies, silent corticotroph tumors were found to have 200-fold higher SSTR1mRNA than nonfunctioning tumors, 17-fold higher than Cushing's disease tumors and 5-fold higher SSTR2mRNA than CD, but lower SSTR5 mRNA than CD (28). Given Pasireotide has demonstrated high binding affinity for SST1, 2, 3 and 5, there is good rationale to investigate the utility of pasireotide therapy of silent corticotroph pituitary tumors.

Our study will take a unique approach to evaluate the efficacy of this therapy. Our Neuroendocrine Unit laboratory, under the direction of Dr. Sharon Wardlaw, has developed an assay for plasma POMC. Utilizing measurement of POMC with this assay, we will investigate the efficacy of pasireotide in lowering POMC levels and determine if POMC measurements can serve as a marker for efficacy of pasireotide therapy for silent corticotroph adenomas. Since change in pituitary tumor size is currently the only marker available for monitoring efficacy of treatment of silent corticotroph tumors, the findings of this study could be an important addition to the treatment of patients with silent corticotroph adenomas.

In our ongoing "Prospective Study of Clinically Nonfunctioning Pituitary tumors" funded by the NIH (DK073040), we are prospectively studying a large cohort (currently 285) of patients who have presented with apparent clinically nonfunctioning pituitary tumors. One AIM of this study has been to identify silent corticotroph pituitary tumors based on measurement of plasma POMC levels. All patients have been screened with POMC measurements and POMC levels have been followed over time in patients who had elevated levels, in many also after surgical removal of the pituitary tumor. A number of patients in this cohort have been identified with levels of POMC above our normal range. Those patients with elevated plasma POMC levels were found to have pituitary tumors positive for ACTH on immunohistochemical analysis. We have also examined another group of patients with known silent corticotroph pituitary tumors and some of these patients have been found to have elevated plasma POMC levels. We hypothesize based on the rationale described above that these patients with clinically silent corticotroph pituitary tumors (ACTH positive on pathology) and elevated POMC levels in plasma will respond to pasireotide therapy. Detection of a lowering of the increased plasma levels of POMC by pasireotide would show that POMC measurement is a clinically relevant marker to follow during pasireotide treatment of silent corticotroph tumors. POMC levels could also

serve as a marker that identifies patients in whom pasireotide would be more likely to be effective. Although we do not have evidence yet that pasireotide will produce shrinkage of silent corticotroph tumors, POMC lowering may be associated with tumor shrinkage since somatostatin analog therapy typically produces tumor shrinkage when the biomarker of the tumor is suppressed reflecting tumor cell suppression. This will be tested in this study by examining tumor size changes along that of POMC levels in patients with silent corticotroph tumors.

Thus, our preliminary results suggest that plasma POMC levels will be a useful marker for silent corticotroph pituitary tumors. In this project, we will examine the use of plasma POMC level as a marker for the effectiveness of medical treatment of silent corticotroph tumors with Pasireotide.

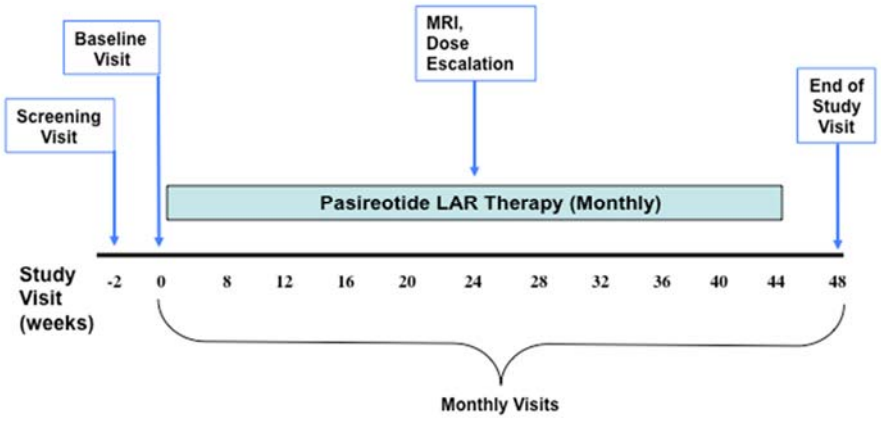
2.2 Study Objectives

	Objective	**Endpoint**
Primary	To determine the efficacy of Pasireotide LAR to suppress plasma levels of POMC in patients with silent corticotroph pituitary tumors.	Change in plasma POMC levels from baseline to 12 months of Pasireotide LAR treatment.
Secondary/Exploratory	To determine the effect of Pasireotide LAR therapy on pituitary tumor volume in patients with silent corticotroph pituitary tumors.	Changes in pituitary tumor volume from baseline to 12 months of Pasireotide LAR Treatment.

3 INVESTIGATIONAL PLAN

3.1. Overall study design

This is an open-label, 12-month pilot study of Pasireotide LAR therapy of 10 patients with silent corticotroph pituitary tumors.



Pasireotide LAR 40 mg will be administered monthly. Baseline and monthly visits on therapy will monitor plasma levels of POMC, other pituitary function, safety labs, glucose tolerance, physical examination, and visual fields. Pituitary MRI will be done at baseline, 6 months and 12 months of therapy.

The starting dose is Pasireotide LAR 40 mg/month IM, this will be increased to 60 mg/month at 6 months if a fall in POMC levels and/or tumor shrinkage are not attained. LAR will be administered monthly with the last injection at Week 44.

3.2 Study population

Ten (10) patients with clinically nonfunctioning pituitary tumors of the silent corticotroph tumor subtype will be studied in this protocol. Males and females are eligible for enrollment. Subjects ages 18 – 80 are eligible for enrollment. Patients will be drawn from primarily from our cohort of 285 patients will clinically nonfunctioning pituitary tumors followed in our prospective study. Patients will also be recruited from subjects treated at our Neuroendocrine Unit and Pituitary Center for who are known to have silent corticotroph pituitary tumors. The investigator will ensure that only patients who meet all

the following inclusion and none of the exclusion criteria are offered treatment in the study. The investigator will maintain an enrollment log of screened/enrolled subjects.

3.2.1 Inclusion and exclusion criteria

Inclusion criteria:

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Adults (males and females) (ages18- 80 years) with a diagnosis of a clinically nonfunctioning pituitary tumor of the silent corticotroph tumor type (i.e. positive ACTH staining on immunohistochemical staining of the pituitary tumor obtained at surgery)
2. Plasma POMC level within or greater than the upper limit of normal
3. Prior pituitary tumor surgery with residual or recurrent pituitary tumor visible on MRI scan that is ≥ 5 mm from the optic chiasm.
4. Surgical resection of the pituitary adenoma must have occurred two or more months prior to baseline visit.
5. If patients have undergone pituitary radiotherapy they must have completed their course of radiotherapy at least 2 months prior to study screening
6. No prior somatostatin analog therapy
7. No concurrent use of dopamine agonist therapy
8. No active malignancy
9. Stable pituitary hormone supplements (x 2 months) prior to baseline visit
10. Sign and date an informed consent document indicating that the subject has been informed of and agrees to all pertinent aspects of the trial

Exclusion criteria

Subjects must not meet any of the following exclusion criteria to be eligible for enrollment into the study:

1. Patients with Cushing's disease (biochemical evidence of hypercortisolism).
2. Patients with compression of the optic chiasm causing any visual field defect that requires surgical intervention
3. Diabetic patients with poor glycemic control as evidenced by HbA1c >8%
4. Patients who are hypothyroid or adrenally insufficient and not on adequate replacement therapy
5. Patients with symptomatic cholelithiasis and acute or chronic pancreatitis
6. Patients with risk factors for torsade de pointes, i.e. patients with a baseline QTcF >450 ms in males, and >460 ms in females

7. Hypokalaemia, hypomagnesaemia, uncontrolled hypothyroidism, family history of long QT syndrome or concomitant medications with known risk of Torsades de pointes (TdP). Drugs with possible risk of TdP should be avoided whenever feasible.
8. Patients who have congestive heart failure (NYHA Class III or IV), unstable angina, sustained ventricular tachycardia, clinically significant bradycardia, advanced heart block, history of acute MI less than one year prior to study entry or clinically significant impairment in cardiovascular function
9. 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
10. Patients with liver disease such as cirrhosis, chronic active hepatitis, or chronic persistent hepatitis, or patients with ALT/AST > 2.0 X ULN, serum bilirubin >2.0 X ULN
11. Presence of Hepatitis B surface antigen (HbsAg) or Hepatitis C antibody test (anti-HCV)
12. Patients with serum creatinine >2.0 X ULN
13. Patients with WBC <3 X 10^9/L; Hb 90% < LLN; PLT <100 X 10^9/L
14. Patients with the presence of active or suspected acute or chronic uncontrolled infection
15. Patients who have undergone major surgery/surgical therapy for any cause within 4 weeks prior screening
16. 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)
17. History of syncope or family history of idiopathic sudden death
18. History of immunocompromise, including a positive HIV test result (ELISA and Western blot)
19. Sexually active males unless they use a condom during intercourse while taking drug and for 3 months following last dose of pasireotide and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.
20. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive urine pregnancy test
21. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and 3 months following last dose of pasireotide. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment

- Male sterilization (at least 6 months prior to screening). For female subjects on the study the vasectomized male partner should be the sole partner for that subject
- Combination of any two of the following (a+b or a+c, or b+c):
  a) Use of oral, injected or implanted hormonal methods of contraception or other
  forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
  b) Placement of an intrauterine device (IUD) or intrauterine system (IUS)
  c) Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

- In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.
- Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

3.3. Treatment

3.3.1. Investigational Therapy

Patients who have provided written informed consent will undergo screening procedures. Once eligibility is established patients will begin therapy with Pasireotide LAR 40 mg.

Pasireotide LAR 40 mg will be administered as intra-muscular (i.m.) intragluteal injections injections every 4 weeks. Uptitration will occur to Pasireotide LAR 60 mg after 6 months of therapy with Pasireotide LAR 40 mg if POMC level has not been suppressed and/or pituitary tumor shrinkage has not occurred. For patient receiving 40 mg dose down-titration to 20 mg is permitted for patients who do not tolerate 40 mg. For patients who are up-titrated to the 60 mg dose down-titration to 40 mg is permitted if tolerability issues occur on this higher dose.

Medication labels will comply with legal requirements and be printed in English. The storage conditions for study drug will be described on the medication label.

Should anti-diabetic treatment be needed during the study (see adverse events) this will be provided by the investigator according to standard clinical practice for diabetes care. The order of initiation of anti-diabetic therapy is expected to be, but is not prescribed as part of this protocol:

- Metformin at individual doses starting from 1000 mg/day to maximum dose according to the approved package insert and depending on the patient tolerability
- Sitagliptin 50 or 100 mg administered orally once a day

• Insulin administered s.c. according to package insert

3.3.2. Concomitant therapy

Chronic maintenance medications will continue on their current therapy during the course of the study. The patient will be told to notify the investigational site about any new medications he/she takes after the start of the study drug. Any changes in the dose of any medication the patient was taking prior to or during the study have to be notified as well. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered during the study will be documented in the subject records.

The use of drugs that may stimulate GH secretion such as L-dopa or arginine is not permitted. In addition, the use of the drugs listed in the exclusion criteria is not permitted.

Limited published data indicate that somatostatin analogs might decrease the metabolic clearance of compounds known to be metabolized by cytochrome P450 enzymes, which may be due to the suppression of growth hormones. Since it cannot be excluded that pasireotide may have this effect, other drugs mainly metabolized by CYP3A4 and which have a low therapeutic index (e.g., quinidine, terfenadine) should therefore be used with caution. Consumption of fruits that may inhibit the CYP3A4 system (star fruit, papaya, pomegranate and grapefruit) will also be advised against during the study.

Somatostatin analogs have been associated with alterations in nutrient absorption, so pasireotide may have an effect on absorption of orally administered drugs. Concomitant administration with cyclosporine may decrease blood levels of cyclosporine and result in transplant rejection.
Patients receiving insulin, oral hypoglycemic agents, beta-blockers, calcium channel blockers, or agents to control fluid and electrolyte balance, may require dose adjustments of these therapeutic agents. Any anti-diabetic medications that the patient takes during the study will be listed in study-specific source documents. If oral contraception is used, the patient must have been practicing this method of birth control for at least three months prior to enrollment and must agree to continue the oral contraceptive throughout the course of the study and for 3 months after pasireotide LAR last dose.

Prohibited concomitant medications
The use of concomitant medication with a known risk of Torsades de Pointes (TdP) is prohibited. In case a patient needs to take medication with a known risk of TdP, it will require study drug discontinuation prior to starting the medication. Appendix 1 lists QT prolonging medications.

Interruption or discontinuation of treatment

Patients who experience an enlargement of their pituitary tumor or any clinical signs consider to represent progression of the tumor while on Pasireotide LAR therapy will be withdrawn from the study by the investigator. Patients that experience severe or life-threatening hyperglycemia (diabetic ketoacidosis, hyperosmolar coma), develop jaundice, hepatitis or other primary hepatic dysfunction will be discontinued from the study. Patients who develop an allergic reaction to Pasireotide LAR® Depot will be discontinued. It will be documented whether or not each patient completed the clinical study. If for any patient either study treatment or observations were discontinued the reason will be recorded. Reasons that a patient may discontinue participation in a clinical study are considered to constitute one of the following:

1. adverse event(s)
2. abnormal laboratory value(s)
3. abnormal test procedure result(s)

4. subject's condition no longer requires study treatment
5. protocol violation
6. subject withdrew consent
7. lost to follow-up
8. administrative problems
9. death

Any patient who receives at least one dose of trial medication will be included in the safety analysis.

3.4. Visit schedule and assessments

3.4.1 Evaluation and Visit Schedule

Protocol Activities and Forms to be Completed	**SV**	**BV**													
Week of Visit (± 7 days)	**-4 to -2**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**54**
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15
Informed Consent	X														
Demography	X														
Inclusion/ Exclusion Criteria	X	X													
Medical History/ Current & Past Medications	X	X													
Concomitant Medication History	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X														
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vitals (temp, blood pressure, pulse)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HRQoL, EQ- 5D- 5L, Cushing QoL, Beck Depression Inventory		X						X					X		
Study Drug Administration (Pasireotide LAR)		X	X	X	X	X	X	X	X	X	X	X	X		
Pasireotide LAR Dose Escalation								**X**							
HbA1c	X							X						X	
Fasting plasma glucose		X	X	X	X	X	X	X	X	X	X	X	X	X	
Fasting Insulin		X	X	X	X	X	X	X	X	X	X	X	X	X	

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15
OGTT (75 gm)		X					X							X	
CBC (w/ WBC differential)	X			X			X			X				X	
Hepatic Function Panel (AST, ALT, Bilirubins, AlkPhos)	X			X			X			X				X	
Basic Metabolic Panel (Na, K, Cl, HCO3, BUN, Cr, Ca)	X			X			X			X				X	
Serum Cortisol	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Plasma POMC	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Plasma ACTH	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Thyroid Panel (Free T4, TSH)	X														
Coagulation (PT, PTT)	X						X							X	
Serum & Plasma Bank	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X							X						X	
Urine Pregnancy	X														
24 Hr Urinanry Free Cortisol and Creatinine	X														
Salivary Cortisol (late night)(x5)	X							X						X	
Pituitary MRI w/ contrast	X							X						X	
Gallbladder Ultrasound and reading	X													X	
12 Lead ECG and reading	X	X	X	X			X			X				X	

3.4.2. Safety assessments

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, as well as regular monitoring of blood chemistries, and the regular measurement of vital signs as well as physical examinations and EKGs. Laboratory evaluations include clinical chemistries including BUN, creatinine, electrolytes, serum glucose, liver function tests to be performed in the CUMC/NY Presbyterian Hospital clinical laboratory. Safety assessments will be ongoing throughout the study and be conducted by the Sponsor-Investigator. A follow up visit 8 weeks after the final study visit will be conducted for a safety follow up.

Adverse events

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded in study-specific source documents and followed as appropriate. An adverse event is any undesirable sign, symptom or medical condition occurring after starting study drug (or therapy) even if the event is not considered to be related to study drug (or therapy). Study drug (or therapy) includes the drug (or therapy) under evaluation, and any reference or placebo drug (or therapy) given during any phase of the trial.

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen or become more frequent after starting study treatment. Adverse events occurring before starting study treatment but after signing the informed consent form will be recorded in the subject records. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy, and will be recorded in study-specific Adverse Events source documents.
As far as possible, each adverse event will also be described by:

1. its duration (start and end dates),
2. the severity grade (mild, moderate, severe)
3. its relationship to the study drug (suspected / not suspected),
4. the action(s) taken and, as relevant, the outcome.

Guidelines for treatment of patients experiencing AEs (Per CTCAE V4.03)

Medication	Adverse event	Action
Pasireotide LAR i.m.	AE CTC grade ≤ 2	No drug adjustments

Medication	Adverse event	Action
	AE CTC grade ≥ 3 and assessed as study drug related	Reduce pasireotide LAR i.m. dose by 20 mg. If the AE improves to grade ≤ 2 before the next administration, increase dose back to the prior dose. If the dose is increased and the AE recurs at a grade ≥ 3, the dose should be reduced back to 20 mg. Down-titration should proceed similarly if patients have been uptitrated to 60 mg per month with down-titrations proceeding from 40 mg and then to 20 mg as indicated. The patient should stay on this lower dose if clinical benefits are maintained. If the AE does not improve to grade ≤ 2, the dose is to be reduced further if clinical benefits are maintained. If the AE does not improve to grade ≤ 2 on the minimum study dose, the treatment should be stopped. The patient should be discontinued and followed up for safety.

SPECIAL MONITORING FOR ADVERSE EVENTS

QT

- **QT 480 msec < QTcF ≤ 500 msec**
  If at any visit a 480 msec < QTcF ≤ 500 msec is observed for a first time for a patient at a given dose level, the following steps will be taken. A cardiology consultation will be sought as soon as practical but within 7 days of the initial finding of abnormal ECG and the cardiologist must re-evaluate the ECG. The study treatment will be postponed until a cardiologist has re-evaluated the ECG.
- If a QTcF > 480 msec is NOT confirmed, no further action needs to be taken.
- If a QTcF > 480 msec is confirmed, a cardiologist must perform a thorough examination (such as reviewing baseline ECG, concurrent medications and performing a cardiovascular examination, including at least a cardiac auscultation) to assess the patient for cardiovascular risk factors.
- If based upon the assessment by the cardiologist, the investigator considers that there is an acute cardiovascular safety risk and that the patient should not continue with study medication, the patient will be discontinued immediately (discontinuation criteria to be followed).
- If following the examination by the cardiologist, the investigator considers that there is no acute cardiovascular safety risk the patient can continue to receive study medication.

- **QTcF > 500msec**
  If at any visit a QTcF > 500msec is observed, the following steps need to be taken:
    - Triplicate ECGs, each 2-3 minutes apart, need to be taken approximately 1 hour after the initial ECG. The mean QTcF from the triplicate ECGs will be determined. If

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

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

Hepatic Safety

- Patients who develop increased transaminase levels will be monitored with a second liver function evaluation to confirm the finding. If the finding is confirmed, the patient will be followed with weekly liver function monitoring (AST, ALT, bilirubin levels, Alkaline phosphatase) until values return to pre-treatment levels.
- If any of the criteria below are observed at any scheduled or unscheduled visit the sponsor will perform a follow up within **72 hours** of awareness of the abnormality:
  - 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
- Hepatic Safety Follow up:
  - Perform liver-directed medical history and physical examination (i.e. assess occupational hazards, concomitant medications including over-the-counter medications, inter-current illness, etc.)
  - Liver chemistry tests: ALT, AST, total bilirubin, (fractionate to direct/indirect bilirubin if total bilirubin is > 2.0 x ULN), Albumin, PT (INR), ALP, and GGT. These tests will be monitored every **3-4 days** until resolution or return to baseline status.
  - Perform hepatitis screen: anti-HAV, IgM (to confirm acute hepatitis A), HbsAg, Anti-HBc, anti-HCV (if positive, PCR viral load should be assessed), Anti-HEV, ANA antibodies, anti-smooth muscle anti-bodies, CMV and EBV
  - Perform abdominal ultrasound (liver and biliary tree)
- Patients may need to be discontinued if the abnormal liver function criteria are met upon LFT retesting or immediately discontinued without LFT retesting in the case of ALT or AST > 8 times the upper limit of normal. Progress reports of the event will be maintained until resolution or return to baseline status.
- If any of these criteria are met and deemed an AE by the investigator, the event will be recorded on in the subjects records as well as the adverse event log; if the event is deemed serious by the investigator, then an SAE will be reported (as described below in SAE reporting procedures). In addition, any clinically significant findings from the physical examination will be recorded in the subjects study records and adverse event log.

Hyperglycemia

- Blood glucose self-monitoring

The Principal Investigator will educate the patient on the signs and symptoms of hyperglycemia. Patients must monitor their fasting blood glucose by finger stick at home at least 3 times per week for the first 4-week treatment with pasireotide or when the dose of pasireotide is increased. If a patient does not have any fasting values above 100mg/dL, monitoring can be decreased to at least 2 times per week from week 4 to week 12 and 1 time every week for the rest of the study. If any values are observed above 100mg/dL, the guidelines based on the current recommendations from the 2012 ADA aiming at a glycemic treatment goal of FPG < 130mg/dL (<7.2mmol/L) will be followed. Appropriate actions such as initiation of anti-hyperglycemic therapy (and referral to diabetes specialist) will be taken by the investigator.

Patients will be required to keep a diary for their blood glucose for appropriate management throughout the study and present the collected data to the principal investigator for evaluation.

Close and frequent monitoring of blood glucose is needed during pasireotide treatment. Intervention for hyperglycemia will be implemented by the Subject's endocrinologist in conjunction with the Sponsor-Investigator as per standard clinical practice in any patient meeting any of the following criteria: FPG > 130mg/dL or HbA1c ≥ 6.5%.

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

Patients with grade 3 hyperglycaemia (FPG value > 250mg/dL; >13.9 mmol/L) at any point in the study will have the dose of pasireotide decreased. Patients who in spite of appropriate therapeutic interventions and despite dose reduction of study drug develop uncontrolled diabetes mellitus and/or consistently high blood glucose values: FPG ≥ 240mg/dL (13.3 mmol/L) or HbA1c value ≥ 10% will require study treatment discontinuation.

3.4.3 Serious adverse events

Information about all serious adverse events will be collected and recorded on study-specific Serious Adverse Event Report source documents. To ensure patient safety each serious adverse event will be reported as described below. A serious adverse event is an undesirable sign, symptom, or medical condition which:

1. is fatal or life-threatening
2. required or prolonged hospitalization
3. results in persistent or significant disability/incapacity
4. constitutes a congenital anomaly or a birth defect
5. are medically significant, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Events **not** considered to be serious adverse events are hospitalizations for the:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen
- treatment on an emergency, outpatient basis for an event **not** fulfilling any of the definitions of serious given above and **not** resulting in hospital admission.

Pregnancy, although not itself a serious adverse event, will also be reported on a serious adverse event form (as described below) and be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities.

3.4.4 Adverse Event Review and Reporting

To ensure patient safety, every adverse event, regardless of relationship to the drug and occurring after the patient has provided informed consent until at least 8 weeks after the patient has stopped study drug administration, will be reviewed by the Sponsor -Investigator. Any event that meets the definition of an Unanticipated Problem (UP) as per the CUMC IRB's UP Policy will be reported promptly, but no later than a week following the occurrence of the event or the PI's knowledge of the event. All adverse events will be reviewed by the Sponsor-Investigator at the time of learning of the adverse event from the study subject, on receipt of a laboratory value or any other source for determination of seriousness and need for actions as described above. All events will be recorded in the subject charts and an Adverse Event log. All SAEs will be reported Novartis per the following specific reporting requirements.

Reporting of SAEs to the drug manufacturer/supplier:

The Sponsor-Investigator will notify the drug manufacturer, Novartis, of all Serious Adverse Events irrespective of causality, encountered in the Clinical Trial **within twenty-four (24) hours of becoming aware of it**. Each such notice will be reported to Novartis on a MedWatch form (http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf) and transmitted to Novartis via fax utilizing a Novartis provided fax cover sheet (Appendix 7.4, Exhibit A). All information about all SAEs will be collected and recorded on this form; all applicable sections of the form will be completed in order to provide a clinically thorough report. The investigator will assess and record the relationship of each SAE to the study treatment. The fax confirmation sheet will be kept with the source documents at the study site.

To ensure patient safety every SAE regardless of suspected occurring after the patient has provided informed consent and until at least 8 weeks (for LAR) or 30 days (s.c.) after the patient has stopped study drug administration will be reported. Any SAEs experienced after this 8 weeks (LAR) or 30 days (s.c.) period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one will be reported separately as a new event. Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new MedWatch Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event will be reported as a follow-up to that event regardless of when it occurs. The follow-up information will describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the current Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification

(IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

Reporting of Unanticipated Problems (UP)

A UP is any incident, experience or outcome involving risk to subjects or others in any human subjects research that meets all of the following criteria:

- Unexpected (in terms of nature, severity or frequency) given (a) the research procedures that are described in the IRB-approval protocol and informed consent document and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in such research (i.e., there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in such research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized (HHS IRB Guidance, Section I).

At the time of the Occurrence of an Unanticipated Problem:

Each UP willbe reported to the IRB, whether or not (a) it is serious or non-serious.

The UP will be reported promptly, but not later than one week following the occurrence of the UP or the PI's acquiring knowledge of the UP.

The Principal Investigator will make the determination as to whether an incident, experience or outcome constitutes a UP.

Each UP will be reported to the IRB using the Unanticipated Problem Report module in Rascal.

The investigator will conclude in the Unanticipated Problem Report whether the protocol and/or consent form(s) should be modified as the result of the UP. If the protocol and/or consent document(s) requires a revision, a modification must be submitted in Rascal.

At the Time of Continuing Review of a Protocol:

At the time of continuing review of a protocol, the Principal Investigator will submit a summary of all UPs that occurred during the review period and since the beginning of the study. The summary for each UP will include:

- The number of subjects who experienced the UP;
- The investigator's determination as to whether or not the UP was serious; and
- The investigator's determination as to the UP's relationship to the study procedures (e.g., definitely related, probably related or possibly related).

4 Statistical methods

4.1. Efficacy assessments

Specific Study Endpoints:
1. Percentage of patients with suppression of POMC level.
2. Percent change from Baseline of POMC level at each visit.
3. Percent change from Baseline of POMC level at final visit.
4. Percent change from baseline in pituitary tumor volume.
5. Change from baseline of fasting insulin or glucose levels or insulin sensitivity indices.
6. Change in HbA1C level

The primary outcome will be differences in POMC from baseline to 12 months after Pasireotide LAR therapy. We will also assess differences in POMC/ACTH ratios from pre to post-treatment. Changes in pituitary tumor size from pre to post-pasireotide therapy will be assessed. Patient characteristics will be summarized by descriptive statistics. Frequencies and percentages for categorical variables and mean, standard deviation, median, minimum and maximum for continuous variables. The paired t-test and Wilcoxon signed test will be used to evaluate the change in POMC level from baseline to final study visit as appropriate. Peptide levels and ratios will be compared by nonparametric approach. Repeated measures ANOVA will also be used to analyze the change in POMC levels over time during pasireotide therapy. Statistical Analysis will be performed by SAS 9.3.

POMC Precursor ELISA:
POMC precursor will be performed by ELISA with antibodies provided by Dr. Anne White. For this assay capture monoclonal antibody is directed against ACTH 10-18 and detection antibody is directed against γ-MSH. Affinity purified human 31K POMC is used for standards. The assay has 100% crossreactivity with 22K pro-ACTH but none with ACTH, α-MSH or γ-MSH (16,29,30). Assay sensitivity is 7.5 fmol/ml. Normal values for this POMC precursor have been preliminary established by our group (14) and a large-scale normal value study for plasma POMC levels is currently being conducted by Dr. Page-Wilson. ACTH will be measured by solid phase, two-site sequential chemiluminescent immunometric assay and cortisol by solid-phase, competitive chemiluminescent enzyme immunoassay (Immulite 1000), UFC by Liquid-Chromotography-Tandem Mass Spectrometry and Late night salivary cortisol by Mass Spectrometry. Insulin will be measured by by immunofluorometric assay (DPC Immulite). Glucose will be determined by automatic hexokinase method.

TUMOR SIZE CALCULATIONS
Pituitary tumors will be classified as microadenoma (<10 mm) or macroadenoma (≥10 mm) and assessed for cavernous sinus invasion (CSI), ICA encasement, and suprasellar and sphenoid extension with MRI. Invasiveness will be defined by Knosp criteria. Tumor volume will be calculated using the formula: 0.5 X width X length X height (mm3).

4.2 Sample size and power considerations

Sample size and power calculation was carried out for percentage change in POMC level from baseline to final study visit based on prior data examining percentage changes in plasma ACTH from before to after Pasireotide treatment in patients with Cushing's disease. In two Cushing's disease studies, percentage lowering of ACTH level was on average 20% with a 15% SD in this change (31,32). This change was clinically significant, it was associated with 100% of subjects having at least 25% reduction in pituitary tumor size and significant reductions in mean 24 urine free cortisol levels (31,32). From these data, we also expect POMC levels to be reduced by 20% with Pasireotide LAR therapy of POMC secreting silent corticotroph tumors. If the true difference from baseline to post-Pasireotide LAR therapy represents a 20% fall in POMC level and SD of this difference is 15% we will be able to reject the null hypothesis that the percentage change in POMC level is 0 with power >90% and 10 pairs of Pasireotide LAR treated patients with a significance level 0.05 using a two-sided paired t-test.

5.0 Protocol amendments, other changes in study conduct

5.1. Protocol amendments

Any change or addition to this protocol requires a written protocol amendment that must be approved by the CUMC IRB.

Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study, require additional approval by the IRB.

Examples of amendments requiring such approval are:

1. an increase above that specified in the protocol in drug dosage or duration of exposure of subjects
2. a significant change in the study design (e.g. addition or deletion of a control group)
3. an increase in the number of invasive procedures to which subjects are exposed
4. addition or deletion of a test procedure for safety monitoring

These requirements for approval should in no way prevent any immediate action from being taken by the Sponsor-Investigator in the interests of preserving the safety of all subjects included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented by her for safety reasons the IRB will be informed within 10 working days.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval but the IRB must be kept informed of such administrative changes.

5.2. Recording of data and retention of documents

Subject data collected from source documents will be documented in an anonymous fashion and the subject will only be identified by the subject number, and by his/her initials. If, as an exception, it is necessary for safety or regulatory reasons to identify the subject, the Sponsor-Investigator will keep this information confidential.

The Sponsor-Investigator will maintain source documents for each patient in the study, consisting of all demographic and medical information, including laboratory data, electrocardiograms, etc, and keep a copy of the signed informed consent form. All information on study-specific source documents will be traceable to these source documents in the patient's file.

Essential documents, as listed below, will be retained by the Sponsor-Investigator for as long as needed to comply with national and international regulations (generally 2 years). The investigator agrees to adhere to the document retention procedures by signing the protocol. Essential documents include:

1. IRB approvals for the study protocol and all amendments
2. all source documents and laboratory records
3. Study-specific source document copies
4. patients' informed consent forms (with study number and title of trial)
5. any other pertinent study document

5.3. Discontinuation of study

See section 3.3.2, page 14.

5.4 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and designed to ensure adherence to Good Clinical Practice, as described in:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
   Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
3. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

5.5 Institutional Review Board

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, will be reviewed by a properly constituted Institutional Review Board. A signed and dated statement that the protocol and informed consent have been approved by the IRB will be obtained prior to study initiation. Any amendments to the protocol, other than administrative ones, will be approved by this committee.

5.6 Informed consent

The investigator will explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent will be given by means of a standard written statement, written in non-technical language. The subject will read and consider the statement before signing and dating it, and will be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained.

Treatments and procedures, as described in the informed consent, that will be paid for as part of this study include the study visits, blood and urine testing, ECGs, gallbladder ultrasound and the study medication Pasireotide LAR. This study will not provide or pay for commercially available medication(s) that subjects are taking and that are part of standard of care. Anti-diabetic medications that may be necessary to start because of Pasireotide LAR using during this study will not be paid for by Novartis or as part of this study. Pituitary MRIs conducted during this study are considered standard of care for patients with pituitary tumors and will be billed to subjects insurance. Other treatments or procedures subjects may receive while they are participating in this study participation and that are not identified in the consent form as being paid for by the study, will not be paid for.

Declaration of Helsinki

The investigator will conduct the trial in accordance with the Declaration of Helsinki.

7 Appendices

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

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

The current list of these drugs can be found on:
http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm

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

Generic Name Class
Bepridil Anti-anginal / heart pain
Amiodarone Anti-arrhythmic / abnormal heart rhythm
Azithromycin Antibiotic
Disopyramide Anti-arrhythmic / abnormal heart rhythm
Dofetilide Anti-arrhythmic / abnormal heart rhythm
Ibutilide Anti-arrhythmic / abnormal heart rhythm
Procainamide Anti-arrhythmic / abnormal heart rhythm
Quinidine Anti-arrhythmic / abnormal heart rhythm
Sotalol Anti-arrhythmic / abnormal heart rhythm
Clarithromycin Antibiotic / bacterial infection
Sparfloxacin Antibiotic / bacterial infection
Erythromycin Antibiotic;GI stimulant / bacterial infection; increase GI motility
Arsenic trioxide Anti-cancer / Leukemia
Astemizole Antihistamine / Allergic rhinitis
Terfenadine Antihistamine / Allergic rhinitis
Pentamidine Anti-infective / pneumocystis pneumonia
Probucol Antilipemic / Hypercholesterolemia
Chloroquine Anti-malarial / malaria infection
Halofantrine Anti-malarial / malaria infection
Domperidone Anti-nausea / nausea
Mesoridazine Anti-psychotic / schizophrenia
Thioridazine Anti-psychotic / schizophrenia
Haloperidol Anti-psychotic / schizophrenia, agitation
Pimozide Anti-psychotic / Tourette's tics
Chlorpromazine Anti-psychotic/ Anti-emetic / schizophrenia/ nausea
Cisapride GI stimulant / heartburn
Levomethadyl Opiate agonist / pain control, narcotic dependence
Methadone Opiate agonist / pain control, narcotic dependence
Droperidol Sedative;Anti-nausea / anesthesia adjunct, nausea

7.2 Appendix 2: Formula to calculate QTcF

The QTcF will be calculated with the following formula:

QTcF = QTInterval / (RRInterval) 1/3

Use the QTInterval and RRInterval provided by the ECG machine.

All calculations should be part of the source documentation in the patients' files.

7.3 Appendix 3: Lifestyle measures in association with anti-diabetic treatments

Lifestyle recommendations from the ADA (ADA 2013)
You have the power to improve and protect your health. With proper nutrition and physical activity and by making good lifestyle choices (like not smoking), you can feel better, stronger, and healthier, and can lower your risk of diseases such as cancer, diabetes, heart disease and stroke.

What is a Healthy Weight?
There's an easy way to find out if your current weight puts you at risk for developing serious diseases. Go to www.diabetes.org/bmi and take the Body Mass Index (BMI) test. The results will help you decide if you need to be concerned about your weight.
The Better You Eat, the Better You Feel

Here are some basic guidelines to help you and your family make healthier food decisions.
• Eat lots of vegetables and fruits.
• Choose whole grain foods over processed grain products. Try brown rice instead of white. Substitute whole wheat bread for white.
• Eat fish 2 – 3 times a week.
• Select leaner cuts of meat like those that end in "loin."
• Remove the skin from chicken and turkey.
• Eat non-fat dairy
• Drink water and calorie-free non-carbonated beverages.
• Use liquid oils for cooking instead of solid fats.
• Cut back on high calorie snacks like chips, cookies, cakes, and regular ice cream. Look for baked chips and reduced calorie snacks. Or have a piece of fruit instead.
• Watch your portion sizes. Even too much "healthy" food can cause weight gain.

Another resource that you might find valuable is the American Diabetes Association's online nutrition tool, My Food Advisor. Here you can find recipes, compare foods, search for healthier alternatives and calculate calories, carbohydrates and other nutrients for a meal, a recipe or a whole day of food.

Tips:
• Compare labels of similar foods, then choose the one with smaller amounts of saturated fat, cholesterol and sodium.
• Adults should eat less than 2400 mg. of sodium per day. If you have high blood pressure, you should aim for even less.
• Try adding herbs and spices in your cooking to take the place of salt for enhancing flavor.

To learn more about comparing foods and making healthier choices, go to www.diabetes.org/myfoodadvisor.

A Little Physical Activity Goes a Long Way

Anything that gets you up and moving is good for you. Here's what it can do:
• Reduce your risk of developing type 2 diabetes
• Reduce your risk of heart disease and stroke
• Lower blood pressure and cholesterol

• Reduce blood glucose (sugar) levels if you have diabetes, which can reduce your risk of developing diabetes-related complications
• Relieve stress
• Help you lose weight
• Give you more energy
• Help you sleep better
• Build stronger bones and muscles

You don't need to go to a gym, play sports or use fancy equipment. Of course, you should talk to your doctor before starting any exercise regimen.

If You Have Diabetes

Eating healthy and staying active are even more important if you have diabetes. Well balanced meals can help keep your glucose (sugar) level as close to normal as possible.

Being active also helps you lower your blood glucose. If you increase your level of physical activity, you may be able to take less insulin or diabetes pills. If you're very inactive, have heart disease or a history of foot ulcers, consult your doctor about safe exercise for you.

Check your blood glucose before exercising. If it's under 100 mg/dl, eat some fruit, crackers or have a glass of milk or juice. Check it again after exercising to learn how your blood sugar responds to exercise.

7.4 Novartis Adverse Event Reporting Forms

EXHIBIT A

NOVARTIS

Interventional Clinical Trial SAE Fax Cover Sheet

To: Local Novartis Drug Safety and Epidemiology Safety Desk *1 877 778 9739*

Investigator contact details:
Name: _____
Fax number : _____
Phone number : _____

Study Name	
Centre Number	
Patient Number	

Relationship between study treatment and event(s) is:

Suspected/Unknown

This document contains important safety information.
If fax is received in error, please forward to 1 877 778 9739

Version 1.0, 01_Jul_2010

NOVARTIS

Interventional Clinical Trial SAE Fax Cover Sheet

To: Local Novartis Drug Safety and Epidemiology Safety Desk *1 877 778 9739*

Investigator contact details:
Name: _____
Fax number : _____
Phone number : _____

Study Name	
Centre Number	
Patient Number	

Relationship between study treatment and event(s) is:

Not Suspected

This document contains important safety information.
If fax is received in error, please forward to 1 877 778 9739

Version 1.0, 01_Jul_2010

7.5 Appendix 5: Patient Quality of Life Questionnaires

EQ-5D-5L Questionnaire

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

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

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

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

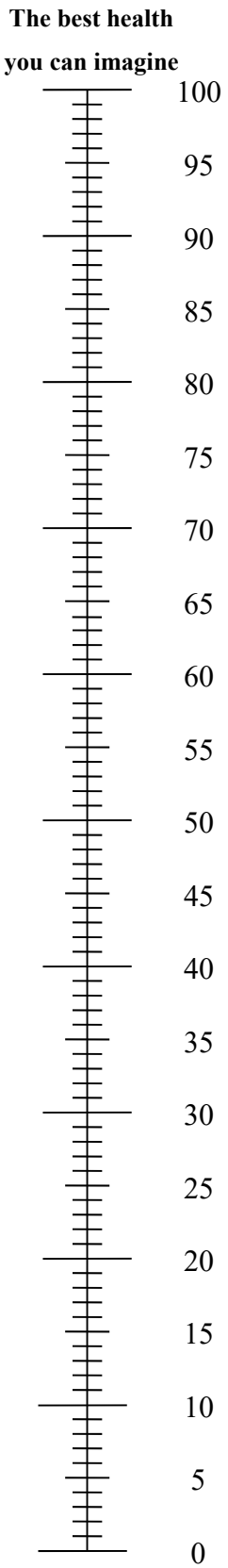
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- **We would like to know how good or bad your health is TODAY.**
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Cushing's Syndrome Quality Of Life Questionnaire

The following sentences refer to what you may think or feel about your Cushing's syndrome. Your answers will help us to know how you feel and how much your illness has interfered in your usual activities in **the past 4 weeks**.

Below each sentence you will find several response choices. Please read each sentence carefully. After reading each sentence, check the box next to the answer that best describes what you think is happening to you.

There are NO right or wrong answers. We are simply interested in what is happening to you because of your Cushing's syndrome.

I have trouble sleeping (I wake up during the night; it takes me a long time to get to sleep, etc.).
☐ Always
☐ Often
☐ Sometimes
☐ Rarely
☐ Never

I have pain that keeps me from leading a normal life.
☐ Always
☐ Often
☐ Sometimes
☐ Rarely
☐ Never

My wounds take a long time to heal.
☐ Always
☐ Often
☐ Sometimes
☐ Rarely
☐ Never

I bruise easily.
☐ Always
☐ Often
☐ Sometimes
☐ Rarely
☐ Never

I am more irritable, I have sudden mood swings and angry outbursts.
☐ Always
☐ Often
☐ Sometimes
☐ Rarely
☐ Never

I have less self-confidence, I feel more insecure.
☐ Always
☐ Often
☐ Sometimes
☐ Rarely
☐ Never

I'm worried about the changes in my physical appearance due to my illness.
☐ Always
☐ Often
☐ Sometimes
☐ Rarely
☐ Never

I feel less like going out or seeing relatives or friends.
☐ Always
☐ Often
☐ Sometimes
☐ Rarely
☐ Never

I have had to give up my social or leisure activities due to my illness.
☐ Always
☐ Often
☐ Sometimes
☐ Rarely
☐ Never

My illness affects my everyday activities such as working or studying.
☐ Always
☐ Often
☐ Sometimes
☐ Rarely
☐ Never
It's difficult for me to remember things.
☐ Always
☐ Often
☐ Sometimes
☐ Rarely
☐ Never

I'm worried about my health in the future.
☐ Always
☐ Often
☐ Sometimes
☐ Rarely
☐ Never

Beck Depression Inventory Questionnaire

This depression inventory can be self-scored. The scoring scale is at the end of the questionnaire.

1.
   0 I do not feel sad.
   1 I feel sad
   2 I am sad all the time and I can't snap out of it.
   3 I am so sad and unhappy that I can't stand it.
2.
   0 I am not particularly discouraged about the future.
   1 I feel discouraged about the future.
   2 I feel I have nothing to look forward to.
   3 I feel the future is hopeless and that things cannot improve.
3.
   0 I do not feel like a failure.
   1 I feel I have failed more than the average person.
   2 As I look back on my life, all I can see is a lot of failures.
   3 I feel I am a complete failure as a person.
4.
   0 I get as much satisfaction out of things as I used to.
   1 I don't enjoy things the way I used to.
   2 I don't get real satisfaction out of anything anymore.
   3 I am dissatisfied or bored with everything.
5.
   0 I don't feel particularly guilty
   1 I feel guilty a good part of the time.
   2 I feel quite guilty most of the time.
   3 I feel guilty all of the time.
6.
   0 I don't feel I am being punished.
   1 I feel I may be punished.
   2 I expect to be punished.
   3 I feel I am being punished.
7.
   0 I don't feel disappointed in myself.
   1 I am disappointed in myself.
   2 I am disgusted with myself.
   3 I hate myself.
8.
   0 I don't feel I am any worse than anybody else.
   1 I am critical of myself for my weaknesses or mistakes.
   2 I blame myself all the time for my faults.
   3 I blame myself for everything bad that happens.
9.
   0 I don't have any thoughts of killing myself.
   1 I have thoughts of killing myself, but I would not carry them out.
   2 I would like to kill myself.

3 I would kill myself if I had the chance.

10.
0 I don't cry any more than usual.
1 I cry more now than I used to.
2 I cry all the time now.
3 I used to be able to cry, but now I can't cry even though I want to.

11.
0 I am no more irritated by things than I ever was.
1 I am slightly more irritated now than usual.
2 I am quite annoyed or irritated a good deal of the time.
3 I feel irritated all the time.

12.
0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

13.
0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions more than I used to.
3 I can't make decisions at all anymore.

14.
0 I don't feel that I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel there are permanent changes in my appearance that make me look unattractive
3 I believe that I look ugly.

15.
0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

16.
0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

17.
0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

18.
0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

19.
0 I haven't lost much weight, if any, lately.
1 I have lost more than five pounds.

2 I have lost more than ten pounds.
3 I have lost more than fifteen pounds.

20.
0 I am no more worried about my health than usual.
1 I am worried about physical problems like aches, pains, upset stomach, or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think of anything else.

21.
0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I have almost no interest in sex.
3 I have lost interest in sex completely.

INTERPRETING THE BECK DEPRESSION INVENTORY

Now that you have completed the questionnaire, add up the score for each of the twenty-one questions by counting the number to the right of each question you marked. The highest possible total for the whole test would be sixty-three. This would mean you circled number three on all twenty-one questions. Since the lowest possible score for each question is zero, the lowest possible score for the test would be zero. This would mean you circles zero on each question.
You can evaluate your depression according to the Table below.

Total Score	Levels of Depression
1-10	These ups and downs are considered normal
11-16	Mild mood disturbance
17-20	Borderline clinical depression
21-30	Moderate depression
31-40	Severe depression
over 40	Extreme depression

PERSISTENT SCORE OF 17 OR ABOVE INDICATES THAT YOU MAY NEED MEDICAL TREATMENT. IF YOU HAVE ANY CARDIAC CONCERNS, PLEASE CONTACT CARDIOVASCULAR INTERVENTIONS, P.A. at 407-894-4880

7.6 Appendix 6: Blood Glucose Diary

Blood Glucose Diary

Subject ID: _____

Diabetes Meds:

_____

DATE	Breakfast	Time of the last meal	Lunch	Time of the last meal	Dinner	Time of the last meal	Before bed	Time of the last meal	Comment

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