NOVARTIS

Clinical Development

Pasireotide, SOM230

Protocol CSOM230B2219 / NCT02060383

A multi-center, randomized, open-label, Phase IV study to investigate the management of pasireotide-induced hyperglycemia with incretin based therapy or insulin in adult patients with Cushing's disease or acromegaly

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List of abbreviations

ACTH	Adrenocorticotropic hormone
ADA	American Diabetes Association
ADME	Absorption Distribution Metabolism Elimination
ADR	Adverse Drug Report
AE	Adverse Event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
Anti-HCV	Hepatitis C antibody
APTT	Activated Partial thromboplastin time
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AUC	Area under the concentration / time curve
b.i.d.	*bis in diem*/twice a day
BLRM	Bayesian Logistic Regression Model
BUN	Blood urea nitrogen
CABG	Coronary Artery Bypass Graft
CDP	Clinical development plan
CI	Confidence interval
CL/F	The total body clearance of drug from the plasma
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSP	Clinical study protocol
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CVA	Cerebrovascular Accident
d	days
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DS&E	Drug Safety and Epidemiology
E	Extension
EAS	Evaluable Analysis Set
EASD	European Association for the Study of Diabetes
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EMA	European Medical Agency
EOP	End of Phase
EW	Extension Week
FAS	Full Analysis Set
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
GEP/NET	Gastroenteropancreatic neuroendocrine tumor
GGT	Gamma-glutamyl transpeptidase
GH	Growth Hormone

[redacted]

GIP	Gastric inhibitory polypeptide
GLP-1	Glucagon-like peptide-1
h	Hour
HbA1c	Hemoglobin A1c
HbsAg	Hepatitis B surface Antigen
hCG	Human chorionic gonadotropin
HVs	Healthy volunteers
i.m.	Intra-muscular
i.v.	intravenous(ly)
IB	Investigator' s Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IGF-1	Insulin-like growth factor 1
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
ITT	Intent to treat
IUD	Intrauterine device
IUS	Intrauterine system
LAR	Long-acting release
LFT	Liver Function Test
MAP	Master Analysis Plan documents project standards in the statistical methods which will be used within the individual clinical trial RAP documentation
MI	Myocardial infarction
MTC	Medullary Thyroid Carcinoma
mUFC	Mean Urine Free Cortisol
NAD	No anti-diabetic
NPH	Neutral protamin hagedorn
NRs	Normal Ranges
o.d.	*omnia die*/once a day
OAD	Oral anti-diabetic
OGTT	Oral glucose tolerance test
p.o.	*per os*/by mouth/orally
PHI	Protected Health Information
PK	Pharmacokinetic
PPG	Post-Prandial glucose
PR	Pre-randomized
PRL	Prolactin
PT	Prothrombin time
PTT	Partial thromboplastin time
q28d	Every 28-days
R	Randomized
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
RAS	Randomized Analysis Set
RBC	Red Blood Cells

[redacted]

REB	Research Ethics Board
s.c.	Sub-cutaneous
SAE	Serious Adverse Event
SAS	Safety analysis set
SC	Steering committee
SE	Standard error
SEC	Specific Safety Event Categories
SMBG	Self-monitored blood glucose
SmPc	Summary of Product Characteristics
SOP	Standard Operating Procedure
SSA	Somatostatin analogues
SST	Somatostatin receptors
$T_{1/2}$	Terminal elimination half-life
T4	Thyroxine
TIA	Transient Ischemic Attack
T_{max}	Time to reach Cmax
TSH	Thyroid stimulating hormone
UFC	Urine free cortisol
ULN	Upper Limit of Normal
W	Week

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Patient Number (Patient No.)	A unique identifying number assigned to each patient/healthy volunteer who enrolls in the study
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

[redacted]

Amendment 3 (17-Mar-2017)

Amendment rationale

1. Clarification regarding the protocol visits included in the 28-day Safety follow-up for Cushing's disease patients receiving pasireotide s.c and the 84-day Safety follow-up for acromegaly patients receiving pasireotide LAR as follows:
   - Eligible patients as per protocol who are transitioning to a roll-over study or local access program will not be required to perform the safety follow-up visit (779) as patients will continue to be monitored for safety.
   - Eligible patients as per protocol who are transitioning to commercial drug will be required to perform the safety follow-up visit (779).
2. Re-insertion of the missing Figure 6-1 QT Prolongation Safety Management.
3. Allow a ± 3 day visit window for Cushing's patients. Visit windows for Acromegaly patients will remain unchanged as per Table 7-1.

Changes to the protocol sections:

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

Section 4.1 Description of core phase, paragraph 7 – revised to "All patients who will not continue pasireotide treatment or patients who will transition to commercial drug will have the safety follow-up visit after the Core (or Extension) End Of Phase (EOP) visit, which will be 28 days after the last pasireotide s.c. dose or 84 days after the last pasireotide LAR dose."

Section 4.2 Extension phase

Revised paragraph 2: "Both non-randomized patients who reached Visit 6 (Pre-randomized-W12) - end of pre-randomization phase and randomized patients who reached Visit 14 (Randomized-W14) - end of randomization phase who have completed their Core EOP visit will be allowed to continue on to the extension phase of the study if they fulfill all of the following"

- Revised paragraph 3: "Patients who withdraw consent from the core phase (pre-randomization or randomization phase) cannot participate in the extension phase."
- Added: "Patients who discontinue prematurely from the core phase cannot participate in the extension phase"
- Added "For all patients, the EOP visit (778) will be performed. However, for patients transitioning to a roll-over study or local access program, the Safety follow-up visit (779) 28 days after the last pasireotide s.c. dose or 84 days after the last pasireotide LAR dose is not required. Patients will continue to be monitored for safety while participating in either the roll-over study or local access program.

Refer to the eCRF Completion Guidelines for further instructions."

[redacted]

Section 6.1.3 Treatment duration – added statement

Revision to paragraph 3:

Patients who are in the extension phase, who continue to receive clinical benefit as assessed by the investigator, will have the opportunity to receive pasireotide either commercially if available or via a roll-over study or local access program if available in order to continue their treatment with pasireotide.

For all patients, the EOP visit (778) will be performed. This includes patients who transition to commercial drug, the Safety follow-up visit (779) 28 days after the last pasireotide s.c. dose or 84 days after the last pasireotide LAR dose is required.

However, for patients who transition to a roll- over study or local access program, the Safety follow-up visit (779) 28 days after the last pasireotide s.c. dose or 84 days after the last pasireotide LAR dose is not required. Patients will continue to be monitored for safety while participating in either the roll-over study or local access program.

Section 6.2.3.2 QT Prolongation – re-inserted and changed Figure title

Figure 6-1 - QT Prolongation Safety Management was inadvertently deleted in Amendment 2.

Section 7.1 Study flow and visit schedule – added

"± 3-day visit window will be allowed for Cushing's patients. Visit windows for Acromegaly patients will remain unchanged as per Table 7-1".

Section 7.1.3 End of treatment visit including study completion and premature withdrawal – revised end of paragraph 1

"These patients should then return for an End of Study/Follow-up visit as described in Section 7.1.4 and complete the EOS Visit assessments and Study Completion eCRF. Patients continuing pasireotide treatment through a roll-over study or local access program will not return for an End of Study/Follow-up visit as their safety will be monitored.

Section 7.1.3 End of treatment visit including study completion and premature withdrawal – revised end of paragraph 3

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

Section 7.1.4 Follow-up and End of Study Visit – revised to

"All patients must have safety evaluations and complete the EOS assessments at the EOS visit 28 days after the last dose of pasireotide s.c or 84 days after the last dose of pasireotide LAR. Patients continuing pasireotide treatment through a roll-over study or local access program will not return for an End of Study/Follow-up visit as their safety will be monitored."

Refer to the eCRF Completion Guidelines for further instructions.

[redacted]

IRBs/IECs

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

The changes described in this amended protocol are non-substantial and do not require IRB/IEC approval prior to implementation.

[redacted]

Amendment 2 (29-Sep-2016)

Rationale

As of 9-Sep-2016, 166 patients have been enrolled (49 patients with Cushing's disease and 117 patients with acromegaly). Of the 166 patients enrolled in the trial, out of the planned 79 patients have been randomized (20 Cushing's disease and 30 acromegaly).

The rationale of this amendment 2 is to remove the protocol requirement to randomize the equal number of patients with Cushing's disease and Acromegaly (a total of 79 patients).

In protocol amendment 1, the target was to randomize 79 patients (42 in Cushing's disease and 37 in acromegaly) to obtain 68 randomized patients (34 with Cushing's disease and 34 with acromegaly, who completed at least 8-week randomized treatment without any rescue medication).

Cushing's disease is a rare disease with a low incidence and prevalence and the recruitment of these patients in clinical studies is challenging. In the present study, the availability of this patient population has been lower than expected and consequently, more patients with acromegaly than patients with Cushing's disease are being screened and ultimately randomized. Despite the fact that patients with Cushing's disease and Acromegaly exhibit insulin resistance and metabolic abnormalities secondary to different mechanisms and that the severity of hyperglycemia might differ, the effect of pasireotide on glucose metabolism is expected to be the same in both populations (i.e. increase of blood glucose levels by decreasing insulin and incretin secretion). Therefore, the proportion of randomized patients from each disease group is not expected to affect the scientific value of the study.

Additional changes for clarification and corrections are included in this amendment:

- Since more patients than the originally 133 planned have been enrolled without achieving the planned 79 randomized patients, language has been modified to ensure that the number of enrolled patients will be based on the actual randomization rate
- Added the updated DILI standard language to Section 6.2.3.3 Hepatic safety management. This language update was made across Oncology Novartis programs
- Clarified that all patients are to call the site immediately if results of any single occurrence of self-monitored fasting blood glucose is > 250 mg/dL, in order to allow for appropriate management of hyperglycemia
- Added IWRS/IRT Registration in Table 7-2 Extension Phase Visit Evaluation Schedule
- Corrected and removed the PK sample collection which is not applicable in this study from Figure 6-2 LFT management algorithm

[redacted]

Changes to the protocol sections:

1. Protocol summary - Population and Section 5.1 Patient Population:
   a. Removed the need to enroll approximately 133 patients. The total number of enrolled patients is defined based on the regular monitoring of the actual randomization rate
   b. Removed the need to randomize equal number of Cushing's disease patients (34) and Acromegaly patients (34).
2. Section 4.1.1 Pre-randomized period: Clarified that patients are to report immediately results of a single occurrence self-monitored fasting blood glucose > 250 mg/dL
3. Section 6.2.3.3 Hepatic safety management: Updated with the DILI standard language
4. Table 7-2 Extension Phase Visit Evaluation Schedule: Added IWRS/IRT Registration in the table
5. Section 10.8 Sample size calculation:
   a. Removed the need to enroll approximately 133 patients. The total number of enrolled patients is defined based on the regular monitoring of the actual randomization rate
   b. Removed the need is to randomize equal number of Cushing's disease patients (34) and Acromegaly patients (34). This amendment releases this restriction.
   c. Clarified randomized patients who are evaluable
   d. Modified the total enrollment which will be based on estimate of the actual randomization rate
6. Section 14.2 Appendix 2: Formula to calculate QTcF – added the msec. unit.

Changes will have no significant implications for participants or for the conduct, management or scientific value of the study, and can be regarded as "non-substantial" or "administrative".

The changes described in this amended protocol are non-substantial and do not require IRB/IEC approval prior to implementation.

This amendment does require an update of the ICF.

[redacted]

Amendment 1

As of 23 July 2014, 2 patients have been enrolled on the CSOM230B2219 study.

The main objectives of this protocol amendment are as follows:

- Upon Health Authorities request:
  1. an additional LFT (Liver Function Test) monitoring at Week 1 for the cohort of patients with Cushing's disease on s.c. formulation of pasireotide is included in line with the approved Signifor SmPC (Summary of Product Characteristics)
  2. additional ECG (Electrocardiogram) monitoring at Week 1 in line with the approved Signifor SmPC for the cohort of patients on the s.c. formulation of pasireotide; and at Week 3 in line with the proposed EU SmPC for pasireotide LAR (Long Acting Release) in Acromegaly are included
  3. in line with the ADR (Adverse Drug Report) profile described in the approved labels of anti-diabetic medications used in this study, the following changes are implemented:
     - Exclusion criterion number 13 re-worded to exclude patients with cholelithiasis and acute and chronic pancreatitis.
     - A new exclusion criterion for patients with a family history of MTC (Medullary Thyroid Carcinoma) or MEN2 (Multiple Endocrine Neoplasia syndrome type 2) has been added
     - Exclusion criterion number 18 amended to exclude patients with renal dysfunction as defined by local metformin label (E.g., As per SmPC, creatinine clearance <60 mL/min)
     - Additional pancreatic safety monitoring (lipase and amylase) has been added for all patients.
  4. Patients in Denmark on pasireotide LAR will participate in the overall study (core and extension phases) for up to a maximum of 1 year.
- To ensure that the patients are followed for at least 5 times the elimination half-life ($t_{1/2}$) of study drug, the safety follow-up monitoring was extended to 84 days in patients receiving the pasireotide LAR formulation
- To account for gender differences in QTcF as acknowledged by health authorities, the exclusion criterion at screening was modified to QTcF > 450 ms for males and > 460 ms for females.
- To clarify the washout period for other SSAs, 8 weeks washout for octreotide LAR and lanreotide autogel was specified
- Wash-out period for previous exposure to pasireotide s.c. has been updated to 1 week to minimize unnecessary interruption of pasireotide based on the 16-hour half-life of pasireotide s.c.
- The suggested insulin titration schedule has been updated to align with the study defined glycemic control (mean 3-consecutive daily SMBG <126 mg/dL).
- Clarifications have been included and minor discrepancies have been fixed throughout the protocol.

[redacted]

Please refer to the following section for further details about the amendment.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

- Section 4.1, Section 6.1.3, Section 7.1.3, Section 7.1.4, Section 8.1.1, Section 8.2.2, Section 10.5.3, Figure 4-1, Table 7-1 and Table 7-2: extended the safety follow-up monitoring of patients receiving the LAR formulation to 84 days
- Section 4.1 and Section 4.2: maximum overall study duration for patients in Denmark on pasireotide LAR was added.
- Section 4.1.1 and Section 6.2.3.1: clarified language for self-monitored blood glucose review
- Section 4.1.1: added and clarified language for creatinine clearance and metformin treatment
- Section 4.1.2: Suggested weekly insulin titration schedule has been updated
- Section 5.2: previous exposure to pasireotide wash-out period has been updated
- Section 5.2: Inclusion criterion has been added to consider patients treated with insulin for an acute medical need.
- Section 5.3: clarifications were made to exclusion criteria # 2, #13 and #18 based on the safety profile of the study drug and the anti-diabetic treatment
- Section 5.3: exclusion criterion has been added for known family history of MTC or multiple endocrine neoplasia syndrome type 2 (MEN2)
- Section 5.3: exclusion criterion #14 has been updated based on gender
- Section 6.2.2.1: Metformin dose modification based on renal function added
- Section 6.3.3: Added wash out period for other medical therapies for Cushing's disease or acromegaly
- Section 6.5.3.3: Clarified language related to anti-diabetic treatment
- Section 6.5.3.3: Added information for anti-diabetic treatment according to local regulations
- Table 7-1: table has been updated to correct inconsistencies and visits, PR-Week 1 (401) and PR- Week 3 (402) have been added to align with the approved label for pasireotide s.c. and proposed label for pasireotide LAR
- Section 7.1.3.1: criteria for premature patient withdrawal has been updated with pancreas related discontinuation criteria
- Table 7-3: table has been updated to include lipase and amylase as additional tests
- Section 7.2.3.4.2: Added clarification regarding creatinine clearance
- Section 7.2.3.4.4: Self-monitored blood glucose language clarified
- Section 7.2.3.4.9: Tests related to pancreas function added
- Section 7.2.3.5: Gallbladder ultrasound tests updated to meet pasireotide s.c. and pasireotide LAR study specific criteria

[redacted]

- Table 7-4: ECG tests updated to meet pasireotide s.c. and pasireotide LAR study specific criteria
- Section 8.6: Clarified that there is no DMC for the study
- Section 9.4: randomization and data dispensation information by IRT system included
- Section 10: Timing of final CSR has been updated
- Section 10.1: Definition of FAS & SAS have been clarified
- Section 10.3: Analysis sets for treatment exposure amended from FAS to SAS.
- Section 10.5.3.1: Analysis set and grouping for the analyses listings and tables information has been updated.

IRB/IEC Approval

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

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Protocol summary:

Protocol number	CSOM230B2219
Title	A multi-center, randomized, open-label, Phase IV study to investigate the management of pasireotide-induced hyperglycemia with incretin based therapy or insulin in adult patients with Cushing's disease or acromegaly.
Brief title	An open-label study to investigate the management of pasireotide-induced hyperglycemia with incretin based therapy or insulin in adults patients with Cushing's disease or acromegaly
Sponsor and Clinical Phase	Novartis Phase IV study
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Hyperglycemia was a frequently observed adverse event in the pasireotide clinical studies in both patients with Cushing's disease and acromegaly. The purpose of this trial is to investigate the optimal management of pasireotide-induced hyperglycemia in these patients.
Primary Objective	To evaluate the effect of treatment with incretin based therapy vs. insulin on the 16-week glycemic control in patients with Cushing's disease or acromegaly who develop or worsen hyperglycemia on pasireotide, and cannot be controlled by metformin alone or other background anti-diabetic treatments.
Secondary Objectives	**Objective 1:** To evaluate the overall effect of anti-diabetic intervention on glycemic control in patients with Cushing's disease or acromegaly. **Objective 2:** To evaluate the sustainability of glycemic control in the incretin based therapy arm and the insulin arm in Cushing's disease patients treated with pasireotide s.c. and acromegaly patients treated with pasireotide LAR. **Objective 3:** To evaluate the safety and tolerability of pasireotide in combination with anti-diabetic treatments.
Study design	This is a Phase IV, multi-center, randomized, open-label study. Eligible patients will start pasireotide s.c. for Cushing's disease and pasireotide LAR for acromegaly. Patients currently treated at screening visit with pasireotide s.c. or LAR are eligible if they have an elevated FPG > ULN or a diagnosis of diabetes (FPG ≥ 126 mg/dL on two occasions or HbA1c ≥ 6.5% or a random plasma glucose ≥ 200 mg/dL with classic symptoms of hyperglycemia (polydipsia, polyphagia and polyuria)) during screening period. If previously normo-glycemic patients experience increases in their fasting blood glucose based on pre-defined glycemic criteria while on pasireotide, they will start anti-diabetic treatment using metformin. If they continue to experience increases in their fasting blood glucose within the first 16 weeks, they will be randomized in a 1:1 ratio to receive treatment with incretin based therapy (sitagliptin followed by liraglutide) or insulin for 16 weeks.
Population	The eligible patient population will consist of adult Cushing's disease and acromegaly patients. The study targets to have 68 randomized evaluable patients. The total number of patients will be based on the actual randomization rate which will be monitored regularly.

[redacted]

Key Inclusion criteria	**Cushing's disease population** ● Adult patients (age ≥ 18 y) with confirmed diagnosis of Cushing's disease (persistent/recurrent or *de Novo* patients who are not considered candidates for pituitary surgery). **Acromegaly population** ● Adult patients (age ≥ 18 y) with confirmed diagnosis of acromegaly. *De Novo* patients (with no prior pituitary surgery) can be included if they are not considered candidates for pituitary surgery or have refused surgery. Patients being treated at screening visit with pasireotide should have an elevated FPG > ULN or a diagnosis of diabetes during screening period.
Key Exclusion criteria	● Patients who are receiving other medical therapies for Cushing's disease or acromegaly. All other medical therapies for Cushing's disease or acromegaly have to be discontinued at least 5 times the half-life of the respective preparation before study entry (start of pasireotide). ● Patients who require surgical intervention ● Patients receiving DPP-4 inhibitors or GLP-1 receptor agonists within 4 weeks prior to study entry ● HbA1c > 10 % at screening ● Known hypersensitivity to somatostatin analogues ● History of liver disease ● Cholelithiasis or acute or chronic pancreatitis ● Cardiac or repolarization abnormality ● Life-threatening autoimmune disorders ● Patients who have clinical symptoms of hypothyroidism ● Inadequate bone marrow function
Investigational and reference therapy	Pasireotide s.c. for Cushing's disease, Pasireotide LAR for acromegaly. Anti-diabetic medications: Metformin, Sitagliptin, Liraglutide, Insulin
Efficacy assessments	**Primary efficacy parameter:** Primary efficacy variable is defined as the change in HbA1c (unit in %) from randomization to the subsequent scheduled visit after 16 weeks on randomization in incretin based therapy arm and insulin arm. For patients who require rescue treatment, the last HbA1c assessment before rescue treatment will be used for primary efficacy analysis. **Supportive efficacy parameter:** Supportive efficacy parameter is the same as primary efficacy parameter except that patients taking rescue treatment before the time of assessing the primary endpoint will follow ITT rule, i.e., HbA1c assessment on Core End of Phase (EOP) in each randomized arm will be utilized for analysis regardless of rescue treatment use. **Secondary efficacy parameters:** ● Change in HbA1c and FPG from baseline to Core EOP ● Proportion of patients with an increase in HbA1c ≤ 0.3% ● Change in HbA1c and FPG from randomization overtime ● Proportion of patients that received anti-diabetic rescue treatment
Safety assessments	● Adverse Events ● Laboratory evaluations ● Cardiac assessments (ECG) ● Vital Signs ● Hypoglycemia events ● Thyroid function tests ● Gall bladder ultrasound

[redacted]

Other assessments	None
Data analysis	There is no formal hypothesis testing planned in this study. An estimate of the mean difference of the change from randomization in HbA1c between the two randomized arms will be reported along with 95% confidence interval (CI). Patients will be stratified by their disease and baseline glycemic status. Variance estimation will be based on analysis of variance (ANOVA) model using the two stratification factors (disease and glycemic status at baseline) as well as their anti-diabetic treatment as fixed effects. Patients who are randomized to either incretin based therapy or insulin will be used for primary analysis. For the secondary objectives, categorical variables will be summarized via the number and proportion of patients. Continuous variables will be summarized using relevant descriptive statistics, such as number of patients with measurements, mean, standard deviation, median, minimum, and maximum.
Key words	Cushing's disease, acromegaly, somatostatin, pasireotide, hyperglycemia, incretin based therapy, DPP4 inhibitor, GLP-1 receptor agonist, insulin

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Cushing's disease and acromegaly are both rare but debilitating diseases. Patients with Cushing's disease have excessive adrenocorticotropic hormone (ACTH) secretion from a benign pituitary adenoma, which stimulates the adrenal glands to produce excess cortisol. The hypercortisolemia results in a debilitating condition that affects multiple organ systems. The morbidity includes increased blood pressure, dyslipidemia, insulin resistance, weight gain with central obesity, moon facies, accumulation of fat pad in the supraclavicular and dorsicervical area, osteopenia and osteoporosis, immunosuppression and mental disorders ranging from mood changes to depression and psychosis (Pivonello 2008). The incidence of Cushing's disease ranges from 1-3 patients per million per year. Cushing's disease is associated with severe morbidity and premature mortality and most commonly affects adults aged 20-50 years of age, primarily females.

Acromegaly is characterized by chronic hypersecretion of GH (growth hormone), which, in over 95% of patients, is caused by a GH-secreting pituitary adenoma. The clinical manifestations of acromegaly are due to the peripheral actions of the GH excess and elevated IGF-1 concentrations and/or local tumor mass effect. It is estimated that about 3 out of every million people develop acromegaly each year and that 40 to 60 out of every million people suffer from the disease at any one time (Melmed et al 1998).

Surgical removal of the adenoma is the first line therapy for Cushing's disease. However, the success rate of surgery is between 65-90% for microadenomas (tumors < 1 cm) with recurrence rates between 10 - 20% after 10 years. When surgery and/or irradiation fail, or for those patients for whom such therapies are not an option, the remaining alternatives are pharmacological treatment or bilateral adrenalectomy (Biller et al 2008).

Treatment modalities for acromegaly include surgery, drug treatment or radiotherapy. Transphenoidal surgery is currently the most frequently recommended treatment; however the surgical effectiveness varies depending on expertise in pituitary surgery, both the size and extension of the anatomic mass, and the preoperative levels of GH. Radiation therapy has been used both as a primary treatment and combined with surgery or drugs. It is usually reserved for patients who have tumor remaining after surgery, for patients who are not good candidates for surgery because of other health problems; and for patients who do not respond adequately to surgery and medication. Radiation therapy causes a gradual loss of production of other pituitary hormones with time which can result in the undesired effect of panhypopituitarism. Loss of vision and brain injury, which have been reported, can be complications from radiation treatment (Wass et al 2001). Currently the medical treatment options for acromegaly include somatostatin analogues (SSAs), growth hormone antagonists and dopamine agonists. SSAs have been proven to be safe, well-tolerated and effective and are the medical treatment of choice for acromegalic patients. The currently marketed SSAs are octreotide (Sandostatin®) and lanreotide (Somatuline®). Octreotide has been available for over 15 years and is considered the world-wide gold standard medical treatment for acromegaly.

[redacted]

Pasireotide is a SSA, recently approved in Europe and in the US as a subcutaneous (s.c.) formulation under the trade name Signifor® for the treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed. Pasireotide is also being developed as a long-acting depot formulation (LAR) for the treatment of acromegaly. A phase III study to assess the safety and efficacy of pasireotide LAR vs octreotide LAR in acromegaly was recently completed. The results from this study show that pasireotide LAR is effective and superior to octreotide in treating acromegaly patients. [CSOM230C2305]

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

1.2.1 Overview of pasireotide (SOM230)

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

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

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

1.2.1.1 Clinical experience

1.2.1.1.1 Pasireotide s.c.

The pasireotide s.c. formulation has been evaluated in a total of 19 studies: 11 studies with healthy volunteers, 1 study in patients with varying degrees of hepatic dysfunction, 3 studies with acromegalic patients, 1 study in patients with metastatic carcinoid tumors, and 3 studies in patients with Cushing's disease. A detailed summary of the clinical data (including safety and PK) is provided in the [Investigator's Brochure].

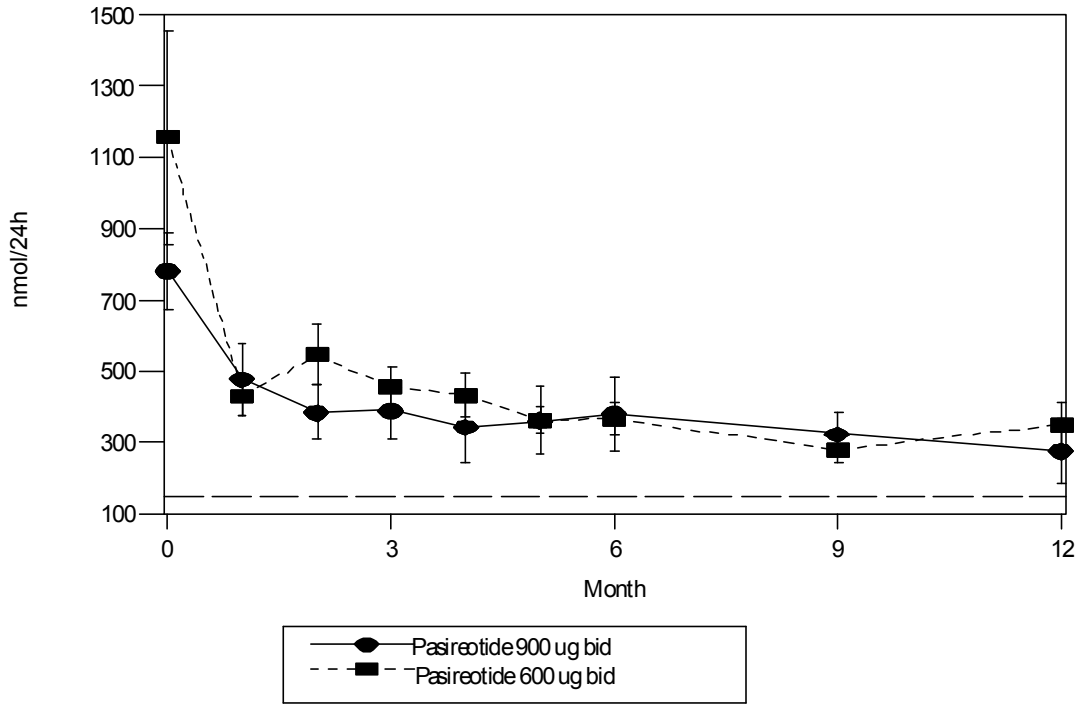
[redacted]

Pasireotide s.c. has demonstrated linear and time-independent pharmacokinetics (PK) in healthy volunteers and patient populations following single- and multiple-dose regiments. The T_{max} was observed to occur within 15-30 minutes. The PK exposures to pasireotide in acromegaly patients were comparable to healthy volunteers. However, the PK exposures to pasireotide in carcinoid syndrome patients and Cushing's disease patients were approximately 2- to 3-fold and 1.4-fold higher relative to healthy volunteers, respectively. The therapeutic doses for Cushing's disease are 600 µg b.i.d. and 900 µg b.i.d. observed from phase II and III studies. [CSOM230B2201, CSOM230B2202, CSOM230B2208, CSOM230B2305]. More detailed description of PK results can be found in the [Investigator's Brochure].

The efficacy of pasireotide s.c. in Cushing's disease is based mainly on the pivotal phase III study CSOM230B2305. The primary objective was to assess the efficacy in terms of response to pasireotide 600 and 900 µg b.i.d. in patients with Cushing's disease as measured by normalization of urine free cortisol (UFC) after 6 months of treatment and whose dose was not increased prior to Month 6.

At Month 6, a total of 12 (15%) of 82 patients in the 600 µg b.i.d. group and 21 (26%) of 80 patients in the 900 µg b.i.d. group achieved mean UFC (mUFC) ≤ ULN. At Month 6, the proportion of patients who were partially controlled (i.e. had a ≥ 50% reduction in UFC but did not achieve mUFC ≤ ULN) was 18.3% and 12.5%, respectively, for the 600 and 900 µg b.i.d. groups. Robust reductions in mUFC occurred relatively quickly, within the first month, and were sustained over the course of Months 6 and 12 (Figure 1-1).

Figure 1-1 Mean (+/- SE) Urinary Free Cortisol (nmol/24h) at time points up to Month 12 by randomized dose group (Full analysis set - Study B2305)



[redacted]

In the pivotal Cushing's disease study [CSOM230B2305], the subcutaneous formulation of pasireotide was well tolerated and the safety profile was generally comparable between the two dose groups. The majority of the AEs reported are consistent with the known adverse drug reactions of SSAs. Most patients (98.1%) experienced at least one AE up to data cut-off and most patients (95.7%) had at least one AE suspected by the investigator to be study drug related. By preferred term, the most frequent (> 15% of patients) AEs overall were diarrhea, nausea, hyperglycemia, cholelithiasis, headache, abdominal pain, fatigue and diabetes mellitus. These gastrointestinal AEs (in general) were transient, and did not result in discontinuation of pasireotide. Patients with Cushing's disease have a known predisposition for hyperglycemia, which was also observed in this study. Elevated glucose was the most frequently reported Grade 3 laboratory abnormality (23.2% of patients). Grade 1, Grade 2 and Grade 4 elevated glucose was observed in 26.0 %, 24.0 % and 0 % of patients respectively. More detailed safety data can be found in the [Investigator's Brochure].

1.2.1.1.2 Pasireotide LAR

The pasireotide LAR has been evaluated in a total of 11 studies: 4 studies in healthy volunteers, 4 studies in both patients with acromegaly and patients with carcinoid disease, 1 study in acromegaly patients and 2 studies in patients with metastatic carcinoid tumors. A detailed summary of the clinical data (including safety and PK) is provided in the [Investigator's Brochure].

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 LAR formulation was comparable to CL/F of the s.c. formulation (4.3-9.0 L/h). $T_{1/2}$ for the LAR formulation was approximately 16 days, suitable for monthly dosing. The relative bioavailability of the 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 post-surgical patients). Pasireotide LAR was as effective as octreotide LAR in reducing tumor volume, improving acromegaly symptoms and ring size, and quality of life [CSOM230C2305].

In the registration study, CSOM230C2305, most patients experienced at least one AE during the core phase of the study. The most frequent event in patients who received pasireotide LAR was diarrhea. By preferred term, AEs that were more frequent (at least 5% difference) in the pasireotide than the octreotide group were all related to glucose metabolism: hyperglycemia,

[redacted]

diabetes mellitus, blood glucose increased, and type 2 diabetes mellitus. Grade 1 elevated glucose as a lab abnormality was observed in 69.6%, Grade 2 in 16.6%, Grade 3 in 9.7% and Grade 4 in 0.6% of patients in the pasireotide group in the study [CSOM230C2305].

2 Rationale

2.1 Study rationale and purpose

Hyperglycemia was a frequently observed adverse event in the pasireotide clinical studies. This study is a post-approval commitment to health authorities to evaluate the effect of incretin based anti-diabetic agents compared to insulin in patients with Cushing's disease treated with pasireotide s.c. or with acromegaly treated with pasireotide LAR. Acromegaly patients are included given that the issue of pasireotide-induced hyperglycemia is not limited to Cushing's disease patients. The purpose of this trial is to investigate the optimal management of pasireotide-induced hyperglycemia in patients with Cushing's disease or acromegaly.

Mechanistic data in healthy volunteers (HVs) indicate that the hyperglycemia associated with pasireotide is due to decreases in insulin secretion (with relatively small inhibition of glucagon) and decreases in incretin hormone GLP-1 and GIP secretion [CSOM230B2216].

A follow-up study [CSOM230B2124] in HVs corroborate that the underlying mechanisms of hyperglycemia following pasireotide s.c. treatment in humans are mainly due to decreased insulin secretion and reduced GLP-1 and GIP incretin secretion with no changes in hepatic or peripheral insulin sensitivity. In this study pasireotide 600 µg b.i.d. was either administered alone or with one of 4 different classes of antihyperglycemic drugs (biguanide [metformin], insulin secretagogue [nateglinide], DPP-4 inhibitor [vildagliptin], and GLP-1 analog [liraglutide]) for 7 days. On Day 7, plasma glucose AUC post-OGTT increased with pasireotide alone. This effect was reduced by 13%, 29%, 45% and 72% with co-administration of metformin, nateglinide, vildagliptin and liraglutide, respectively.

Similarly, compared with pasireotide alone, insulin levels were increased by a mean of 71% and 34% when pasireotide was co-administered with vildagliptin and liraglutide, respectively; only minimal increases were seen after co-administration with metformin (6%) and nateglinide (3%).

These results suggest that incretin based therapies (i.e. GLP-1 analogs and DPP-4 inhibitors) would be most useful in the management of pasireotide-induced hyperglycemia. In view of the pre-existing insulin resistance in patients with Cushing's disease, combination therapy with a biguanide (e.g. metformin) and an incretin enhancer may also be appropriate to treat pasireotide-induced hyperglycemia [CSOM230B2124].

However, the optimal management of pasireotide-induced hyperglycemia in patients is not known.

This study is designed to provide guidance on the optimal treatment algorithm with specific focus on incretin based therapy [*i.e.*, sitagliptin (first DPP-4 inhibitor approved, available in US and EU) followed by liraglutide (long acting GLP-1 receptor agonist available in EU and US)] vs. insulin. In patients who are anti-diabetic treatment naïve, initiation of anti-diabetic

[redacted]

treatment will be based on a confirmed diagnosis of diabetes. The definition of diabetes will be in accordance with the American Diabetes Association (ADA) guidelines: FPG ≥ 126 mg/dL on two occasions or HbA1c ≥ 6.5% or a random plasma glucose ≥ 200 mg/dL with classic symptoms of hyperglycemia (polydipsia, polyphagia and polyuria) (ADA 2013). Consistent with ADA and EASD (European Association for the Study of Diabetes) treatment guidelines, metformin will be used as first line therapy. If additional glycemic control is needed, patients will be randomized to the incretin based therapy (sitagliptin followed by liraglutide) or insulin. Patients not adequately controlled by the incretin based treatment will receive rescue therapy with insulin.

The study aims to demonstrate that pasireotide-induced hyperglycemia can be effectively and safely managed in majority of patients, including those with diabetes at start of pasireotide treatment.

2.2 Rationale for the study design

This study is designed to evaluate the safety and efficacy of intensive hyperglycemia management in patients treated with pasireotide. Patients will be evaluated at baseline and throughout the study by a diabetologist or endocrinologist. The purpose of intensive glucose control is for the patient to reach the glycemic levels recommended by the ADA's standard of care (Nathan et al 2006, ADA 2013). These glycemic goals are: fasting plasma glucose (FPG) 70 to 130 mg/dL, post-prandial glucose (PPG) < 180 mg/dL and HbA1c < 7%. The ADA standard of care for glycemic goals are in accordance with the EASD standards of care for glycemic goals. In accordance with the ADA-EASD treatment guidelines, metformin will be used as first line therapy in this study. Patients needing additional glycemic control will be randomized to the incretin based therapy (sitagliptin followed by liraglutide) or insulin arms. The rationale for using incretin based therapy in this study is based on data from a HV study that suggests that it would be useful in the management of pasireotide-induced hyperglycemia [CSOM230B2124]. The primary efficacy variable in this study [CSOM230B2219] is the change in HbA1c from randomization to approximately 16 weeks post-randomization in the incretin based therapy arm and the insulin arm. Study baseline for other statistical analyses will be at the initiation of pasireotide in the study.

2.3 Rationale for dose and regimen selection

Pasireotide s.c.

The doses used in this study are in line with the approved label in countries where pasireotide s.c is currently marketed. Patients with Cushing's disease in this study will start with a pasireotide initial dose of 600 µg b.i.d by s.c. injection. Eight weeks (2 months) after the start of pasireotide s.c., patients should be evaluated for clinical benefit. After 8 weeks, Cushing's patients who experience a significant reduction in UFC levels should continue to receive pasireotide for as long as benefit is derived. Dose up-titrations to 900 µg s.c. b.i.d after 8 weeks of study treatment will be allowed based on response to treatment, as long as the 600 µg b.i.d dose is well tolerated by the patient and glucose is controlled as recommended by ADA-EASD guidelines. Dose reduction (decrements of 300 µg b.i.d recommended) or discontinuation from the study may occur at any time for safety reasons if this is in the best

[redacted]

interest of the patient. Dose increase and dose reduction is to be based on investigator assessment of risk and benefit for the patient.

Pasireotide LAR

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

Based on data from the CSOM230C2305 study, patients should be evaluated for clinical benefit 3 months (84 days) after the start of pasireotide LAR i.m. therapy. A dose increase to 60 mg/28days will be permitted after 12-weeks of pasireotide LAR treatment if adequate levels of GH and IGF-1 are not observed with the 40 mg dose (no reduction of mean GH level to < 2.5 µg/L and no normalization of IGF-1 to within normal limits (age and sex related)).

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

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
To evaluate the effect of treatment with incretin based therapy vs. insulin on the 16-week glycemic control in patients with Cushing's disease or acromegaly who develop or worsen hyperglycemia on pasireotide, and cannot be controlled by metformin alone or other background anti-diabetic treatments	Change in HbA1c from randomization to approximately 16 weeks in the incretin based therapy arm and insulin arm	
Secondary		Refer to Section 10.5
To evaluate the overall effect of anti-diabetic intervention on glycemic control in patients with Cushing's disease or acromegaly	Change in HbA1c and FPG from baseline to Core EOP (End of Phase) in patients who received pasireotide by treatment group	
To evaluate the sustainability of glycemic control in the incretin based therapy arm and the insulin arm in Cushing's disease patients treated with pasireotide s.c. and acromegaly patients treated with pasireotide LAR	Proportion of patients with ≤ 0.3% HbA1c increase from baseline to Core EOP per randomized arm Change in HbA1c and FPG from randomization over time and to Core EOP (only for FPG) per randomized arm Proportion of patients who required anti-diabetic rescue therapy with insulin per randomized arm	
To evaluate the safety and tolerability of pasireotide in combination with anti-diabetic treatments	Toxicity will be assessed using NCI-CTC criteria version 4.03 for adverse events. Incidence of hypoglycemia events (# of episodes, # of patients) Clinical chemistry, hematology, urinalysis assessments ECGs Special safety assessments: Thyroid function tests, pancreatic safety tests (for anti-diabetic treatments) and gallbladder examinations	

[redacted]

4 Study design

4.1 Description of core phase

This is a Phase IV, multicenter, randomized open-label study to investigate the optimal management of pasireotide-induced hyperglycemia in patients with Cushing's disease or acromegaly. Eligible patients will start pasireotide s.c. for Cushing's disease and pasireotide LAR for acromegaly (See Section 6.1). If they experience increases in their fasting blood glucose as described below, they will start anti-diabetic treatment using metformin. If they continue to experience increases in their fasting blood glucose within the first 16 weeks based on pre-defined glycemic criteria, they will be randomized in a 1:1 ratio to receive treatment with incretin based therapy (sitagliptin followed by liraglutide) or insulin for approximately 16 weeks as described below. The effect on glycemic control will be evaluated up to 32 weeks.

To ensure a similar distribution of patients expected to develop mild/moderate/severe hyperglycemia in both treatment arms, randomization will be stratified according to the levels of the following two factors:

- Disease:
  a. Cushing's disease
  b. Acromegaly
- Glycemic status at baseline:
  a. HbA1c < 7 %
  b. HbA1c ≥ 7%

Patients who are not randomized by Week 16 (of pre-randomized period) will have their Core End of Phase (EOP) visit on Week 16. Patients who are randomized will have their Core EOP visit 16 weeks post-randomization.

Patients who continue to receive clinical benefit will have the option to continue on the extension phase if pasireotide is not commercially available or a local access program is not available and they meet the criteria described in Section 4.2.

The total duration of the core study treatment will be a maximum of 32 weeks (Up to 16 weeks of pre-randomized period + 16 weeks of randomized period). Patients who are not continuing into the extension phase, the last injection of pasireotide s.c. on study will be 1 day prior to Core EOP visit and the last injection of pasireotide LAR on study will be 4 weeks prior to Core EOP visit.

Patients in Denmark on pasireotide LAR will participate in the overall study (core phase + extension phase) for up to a maximum of 1 year.

All patients who will not continue pasireotide treatment or patients who will transition to commercial drug will have the safety follow-up visit after the Core (or Extension) End of Phase (EOP) visit, which will be 28 days after the last pasireotide s.c. dose or 84 days after the last pasireotide LAR dose.

[redacted]

4.1.1 Pre-randomized period

All patients will measure their fasting blood glucose with a glucometer at home daily after study enrollment. At each scheduled visit, the study investigator will review the patient's fasting self-monitored blood glucose (SMBG) values. After their baseline visit, patients will also be instructed to call the site on a weekly basis between visits during the core phase of the study for the investigator to review their SMBG values. Patient will return to the site as soon as possible if the SMBG is elevated and meets the criteria below.

Anti-diabetic treatment naïve patients at study entry

1. If the average fasting SMBG is ≥126 mg/dL on 3 consecutive days, the patient needs to return to the site as soon as possible for FPG to confirm diabetes.
2. If the patient meets the criteria for diabetes (FPG ≥ 126 mg/dL on two occasions or HbA1c ≥ 6.5% or a random plasma glucose ≥ 200 mg/dL with classic symptoms of hyperglycemia [polydipsia, polyphagia and polyuria]) then the patient should be started on metformin 1000 mg/day (twice daily). In patients that cannot tolerate metformin or that have a contraindication to metformin, the patient should be randomized immediately to either the incretin based therapy arm or insulin arm.
3. Metformin dose is to be increased incrementally according to the approved package insert at the discretion of study investigator and patient tolerability.
4. If the average fasting SMBG is ≥ 126 mg/dL on 3 consecutive days at maximum tolerated and stable dose of metformin for not more than 8 weeks, patients will be randomized to either the incretin based therapy arm or insulin arm. Patients will continue metformin at the same dose as at the time of randomization if they continue to tolerate it. The dose of metformin can be reduced at any time based on investigator's judgment for hypoglycemia. Dose of metformin should not be increased after randomization.

Patients on metformin at study entry

- **AND** treated with maximum tolerated and stable dose of metformin: Patients will continue metformin as long as they tolerate it and they have not met the elevated SMBG criteria. If the average fasting SMBG is ≥ 126 mg/dL on 3 consecutive days during pre-randomized period, the patient needs to return to the site as soon as possible to be randomized.
- **AND** treated with sub-maximal tolerated dose of metformin: Patients will continue metformin as long as they tolerate it and have not met the elevated SMBG criteria. If the average fasting SMBG is ≥ 126 mg/dL on 3 consecutive days, the patients' metformin dose needs to be titrated weekly to a maximum tolerated dose (per local approved package insert). Patients with average fasting SMBG ≥ 126 mg/dL on 3 consecutive days on maximal tolerated and stable dose of metformin for not more than 8 weeks should be randomized immediately.

[redacted]

Patients on other allowed oral anti-diabetic agents (OAD) at study entry

- **AND** can tolerate metformin and have no contraindication to metformin should start on metformin after study enrollment. The starting dose of metformin will be based on investigator's judgment. Metformin dose is to be increased incrementally according to the approved package insert at the discretion of study investigator and patient tolerability. Patients may continue their OADs at the discretion of the study investigator. If the average fasting SMBG is ≥ 126 mg/dL on 3 consecutive days on maximal tolerated and stable dose of metformin for not more than 8 weeks, the patient needs to be randomized immediately.
- **AND** cannot tolerate metformin or have a contraindication to metformin can continue on their OADs. Prior to meeting the elevated SMBG criteria patients should continue their OADs as long as they tolerate it. Dose modifications can be made according to approved package insert at the discretion of study investigator and patient tolerability. If the average fasting SMBG is ≥ 126 mg/dL on 3 consecutive days during the pre-randomized period, the patient needs to be randomized immediately. Dose of the OAD should not be increased after randomization. The dose of OAD may be decreased at any time based on investigator judgment for hypoglycemia.

Patients on insulin at study entry

- These patients are not eligible for randomization. They will be followed in a 16-week observational arm to evaluate the effect of pasireotide on blood glucose levels. Patients being treated with a stable dose of insulin (basal with or without prandial insulin) may continue their current dose of insulin (basal with or without prandial insulin). The insulin dose is to be adjusted based on the investigator's discretion to achieve a mean fasting SMBG <126 mg/dl and to prevent hypoglycemia. The dose of insulin may be down-titrated at any point at the discretion of the investigator to prevent hypoglycemia. These patients will end the core phase of the study at the end of the 16-week pre-randomized period.

All patients will be instructed to call the site immediately if results of any single occurrence self-monitored fasting blood glucose are > 250 mg/dL for appropriate management of hyperglycemia. Please see Section 6.2.3.1.1.

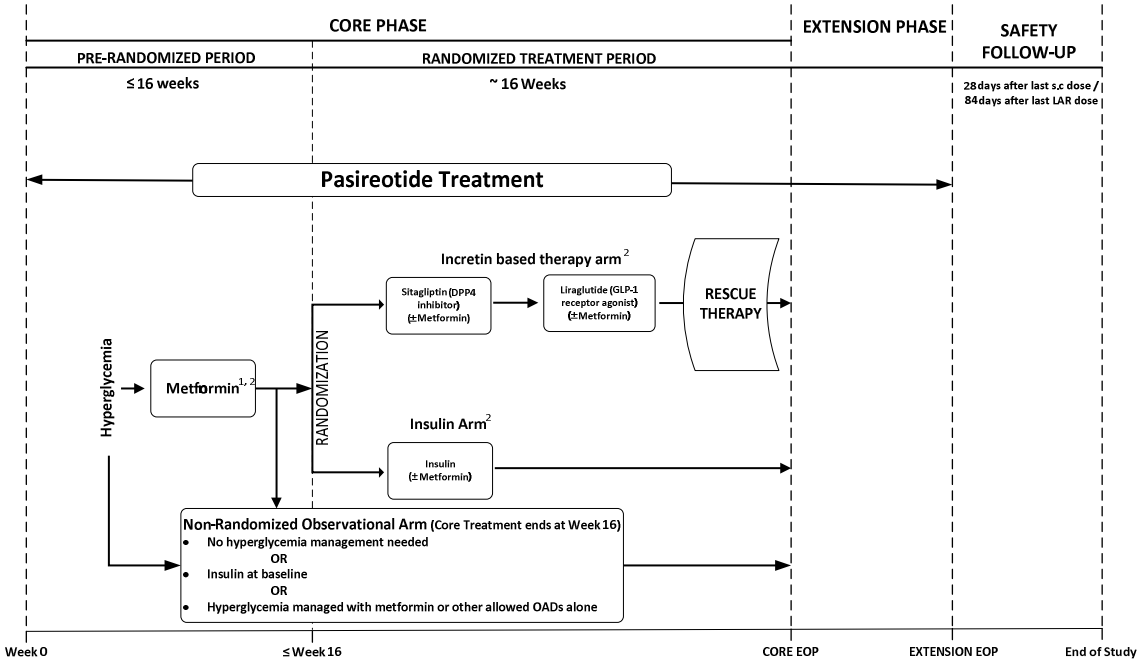
If at any time during the study the patient experiences hypoglycemia, anti-diabetic treatment is to be modified at the discretion of the study investigator. Patients are to be educated on the symptoms and management of hypoglycemia. Please see Section 6.2.3.1.2.

If at any time during the pre-randomization period, the patient develops renal failure or renal dysfunction (creatinine clearance < 60 mL/min or as defined in the local label), metformin should be discontinued and patient can be randomized. Patient can continue on other allowed OADs based upon investigator judgment and in compliance with local prescribing guidelines.

Figure 4-1 shows the general study treatment and anti-diabetic treatment schema.

[redacted]

Figure 4-1 Treatment Schema



[1] Patients that cannot tolerate metformin or have a contraindication to metformin will be randomized immediately if the average fasting SMBG is ≥ 126 mg/dL on 3 consecutive days.
[2] Patients can continue on allowed OADs at the discretion of the investigator.
Note: The patients can continue on the extension phase until the last patient randomized on the core study completes treatment for 16 weeks post-randomization, or when pasireotide is available commercially or when a local access program is available

4.1.2 Randomized period

4.1.2.1 Incretin based therapy arm

Patients randomized to the incretin based arm will start with sitagliptin and will continue metformin and/or other prior anti-diabetic agents at the discretion of the investigator and at the same dose if they continue to tolerate it. The dose of sitagliptin will be adjusted based on patients renal function status as measured by creatinine clearance consistent with the approved package insert. See Section 6.2.2.1 for details. The dose of metformin or other prior anti-diabetic therapy should not be increased after randomization. The dose of metformin or other prior anti-diabetic agent may be decreased at any time based on the investigator's judgment for hypoglycemia.

If the average of fasting SMBG values of 3 consecutive days is ≥126 mg/dL while on stable dose of sitagliptin for at least 6 weeks, sitagliptin will be stopped by the investigator and patients will be switched to liraglutide. Patients may be switched to liraglutide earlier if the average fasting SMBG value on 3 consecutive days is >160 mg/dL. In this event, patients will be instructed to return to the site for an FPG determined by central lab. If FPG value > 160 mg/dL, then the patient will be switched to liraglutide prior to the 6 week dose stabilization period.

[redacted]

After completion of at least 6 week dose stabilization period with liraglutide, patients with fasting SMBG values on 3 consecutive days ≥ 126 mg/dL will be instructed to return to the site for an HbA1c determined by central lab. If HbA1C value >7%, then the patient will be eligible for rescue therapy with addition of insulin. Please see Section 6.1.2 for details on rescue therapy.

Patients may be started on rescue therapy with insulin before the 6-week dose stabilization period with liraglutide if the average fasting SMBG value on 3 consecutive days is >160 mg/dL. In this event, patients will be instructed to return to the site for an FPG determined by central lab. If the FPG >160 mg/dL, then the patient will be started on rescue therapy.

4.1.2.2 Insulin arm

Patients randomized to the insulin arm may start with once daily dose of basal insulin, either insulin NPH (insulin isophane) or insulin glargine or insulin detemir administered at bedtime. The suggested starting dose of insulin is 10 IU/day administered at bedtime with weekly titration to achieve mean 3-consecutive daily SMBG <126 mg/dL. Suggested weekly insulin titration schedule may be as described in Table 4-1.

Table 4-1 Weekly insulin titration schedule

Mean of self-monitored FPG values from preceding 3 days	Increase of insulin dosage (IU/day)
≥ 180 mg/dL (10.0 mmol/L)	6
≥ 140 – <180 mg/dL (7.8 – 10.0 mmol/L)	4
≥ 126 – <140 mg/dL (6.7 – 7.8 mmol/L)	2

The dose of basal insulin may be down-titrated at any point during the randomization period at the discretion of the investigator to prevent hypoglycemia. Addition or treatment with prandial insulin (such as insulin regular or lispro or aspart or glulisine) may be instituted at any time based on investigator discretion to achieve optimal glucose control.

Patients will continue metformin at the same dose as at the time of randomization if they continue to tolerate it. The dose of metformin can be reduced at any time based on investigator judgment for hypoglycemia. Dose of metformin should not be increased after randomization.

Patients receiving insulin at baseline will not be randomized (observational arm) and treated as described in Section 4.1.3.

4.1.3 Non-randomized treatment groups (Observational arms)

Patients who do not develop pasireotide-induced hyperglycemia or worsen their hyperglycemia as specified in Section 4.1.1 within 16 weeks of study entry or they enter the study on insulin will be categorized to one of the following observational groups in the final analysis:

- No anti-diabetic treatment group
- Oral anti-diabetic (OAD) group
- Baseline insulin group

[redacted]

For additional details, please see Section 10.3.

These patients will end the core phase of the study at the end of the 16-week pre-randomized period. Patients who continue to receive clinical benefit will have the option to continue on the extension phase if pasireotide is not commercially available or a local access program is not available and they meet the criteria described in Section 4.2.

4.2 Extension phase

The purpose of the extension phase is to provide pasireotide to patients if it is not commercially available in their country or a local access program is not available to obtain the drug. However, no anti-diabetic medications will be provided by the sponsor during the extension phase unless required by local regulations. Use of anti-diabetic medications during the extension phase will be at the discretion of the study investigator and based on patient's tolerability.

Both non-randomized patients who reached Visit 6 (Pre-randomized-W12) - end of pre-randomization phase and randomized patients who reached Visit 14 (Randomized-W14) - end of randomization phase who have completed their Core EOP visit will be allowed to continue on to the extension phase of the study if they fulfill all of the following:

- the investigator believes the patient is getting significant clinical benefit from treatment with pasireotide
- for female patients of child bearing potential: the patient agrees to continue to use contraception detailed in Section 5.3 throughout the course of the extension phase, and for 1 month following last dose of s.c. or 3 months following last dose of LAR formulation. If oral contraception has been practiced throughout the trial, the patient must continue the oral contraceptive throughout the course of the extension phase, and for 1 month following last dose of s.c. or 3 months following last dose of LAR formulation.
- for male patients: the patient agrees to continue to use condoms throughout the course of the extension phase, and for 1 month following last dose of s.c. or 3 months following last dose of LAR formulation.

Patients who withdraw consent from the core phase (pre-randomization or randomization phase) cannot participate in the extension phase.

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

The patients can continue on the extension phase until the last patient randomized in the core study completes treatment for 16 weeks post-randomization, or when pasireotide is available commercially in their country or when a local access program is available in their country. Patients in Denmark on pasireotide LAR will participate in the overall study (core phase + extension phase) for up to a maximum of 1 year. At the end of the extension phase, all patients will complete their Extension EOP visit. If the patients continue to receive clinical benefit as assessed by the investigator, they will have the opportunity to receive pasireotide either commercially if available or via a roll-over study or a local access program if available in order to continue their treatment with pasireotide.

[redacted]

For all patients, the EOP visit (778) will be performed. However, for patients transitioning to a roll-over study or local access program, the Safety follow-up visit (779) 28 days after the last pasireotide s.c. dose or 84 days after the last pasireotide LAR dose is not required. Patients will continue to be monitored for safety while participating in either the roll-over study or local access program.

Refer to the eCRF Completion Guidelines for further instructions.

4.3 Definition of end of the study

Completion of the study as a whole will occur when last patient last visit is completed or when all patients have completed their end of study (EOS)/ follow-up visit as per Table 7-1 (core phase) and Table 7-2 (extension phase) or have discontinued early.

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in Section 7.1.3.1 for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5 Population

5.1 Patient population

The eligible patient population will consist of adult Cushing's disease and acromegaly patients. The study targets to have 68 randomized evaluable patients. The total number of enrolled patients required to reach the targeted sample size will be based on the estimate of the actual randomization rate which will be monitored regularly.

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

5.2 Inclusion criteria

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

Cushing's disease population

1. Adult patients (age ≥ 18y) with confirmed diagnosis of Cushing's disease (persistent/recurrent or *de Novo* patients who are not considered candidates for pituitary surgery).
2. Patients currently treated at screening visit with pasireotide s.c. should have an elevated FPG > ULN or a diagnosis of diabetes (FPG ≥ 126 mg/dL on two occasions or HbA1c ≥ 6.5% or a random plasma glucose ≥ 200 mg/dL with classic symptoms of hyperglycemia (polydipsia, polyphagia and polyuria)) during screening period.

[redacted]

3. Previous exposure to pasireotide is allowed. In case pasireotide s.c. was discontinued before screening a wash-out period of at least 1 week before study entry (start of pasireotide) has to be followed.

Acromegaly population

4. Adult patients (age ≥ 18 y) with confirmed diagnosis of acromegaly. *De Novo* patients (with no prior pituitary surgery) can be included if they are not considered candidates for pituitary surgery or have refused surgery.
5. Patients currently treated at screening visit with pasireotide LAR should have elevated FPG > ULN or a diagnosis of diabetes (FPG ≥ 126 mg/dL on two occasions or HbA1c ≥ 6.5% or a random plasma glucose ≥ 200 mg/dL with classic symptoms of hyperglycemia (polydipsia, polyphagia and polyuria)) during screening period.
6. Previous exposure to pasireotide is allowed. In case pasireotide LAR was discontinued before screening a wash-out period of at least 3 months before study entry (start of pasireotide) has to be followed.

Inclusion criteria for both Cushing's disease and acromegaly population

7. Patients with either Type 1 or Type 2 diabetes currently being treated with insulin (basal insulin with or without prandial insulin) are eligible for study entry. However, these patients will be treated in the non-randomized observational arm.
8. Patients with Type 2 diabetes being treated with anti-diabetic agents (including metformin) other than incretin based therapies are eligible for study entry and randomization.
9. Written informed consent must be obtained prior to any study related procedure.
10. If patients were treated with insulin only for an acute medical need and insulin was discontinued after that, then a wash-out period of at least 48 hours before study entry (start of pasireotide) has to be followed. These patients will be eligible for randomization.

5.3 Exclusion criteria

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

Cushing's disease population

1. Patients who are receiving other medical therapies for Cushing's disease. All other medical therapies for Cushing's disease have to be discontinued at least 5 times the half-life of the respective preparation before study entry (start of pasireotide).

Acromegaly population

2. Patients who are receiving other medical therapies for acromegaly and not compliant with the following rules:
    - other medical therapies for acromegaly have to be discontinued at least 5 times the elimination half-life ($t_{1/2}$) of the respective preparation before study entry (start of pasireotide);
    - other SSAs (octreotide, lanreotide) have to be discontinued at least 5 times the elimination half-life of the respective formulation before study entry (8 weeks washout for octreotide LAR and lanreotide autogel);

[redacted]

- Dopamine agonists (bromocriptine, cabergoline) or pegvisomant (INN) will only be accepted provided the dose regimen is stable from at least 4 weeks before study entry and throughout the study.

Exclusion criteria for both Cushing's disease and acromegaly population

3. Patients who require surgical intervention
4. Patients receiving DPP-4 inhibitors or GLP-1 receptor agonists within 4 weeks prior to study entry
5. HbA1c >10% at screening
6. Patients with life-threatening diabetic ketoacidosis or diabetic hyperosmolar coma
7. Any major surgery/surgical therapy for any cause within 4 weeks of signing the informed consent (patients must recover from the surgery and be in good clinical condition before entering the study).
8. Participation in any clinical protocol and/or receiving an investigational drug within 4 weeks prior to dosing or longer (a minimal wash out of 5 $t_{1/2}$ of the investigational drug is mandatory and local regulation should be followed).
9. Known hypersensitivity to somatostatin analogues.
10. Patients who are hypothyroid and have clinical symptoms of hypothyroidism despite adequate replacement therapy
11. Life-threatening autoimmune disorders
12. History of liver disease, such as severe hepatic impairment (Child-Pugh C, cirrhosis, or chronic active hepatitis B or C [presence of hepatitis B surface antigen (HbsAg) or hepatitis C antibody (anti-HCV)]).
13. Cholelithiasis acute or chronic pancreatitis.
14. Cardiac or repolarization abnormality, including any of the following:
    - Screening QTcF>450 ms for males and >460 ms for females (See Appendix 2)
    - History of syncope, family history of idiopathic sudden death, family history of congenital long QT syndrome or diagnosis of congenital long QT syndrome.
    - Sustained or clinically significant cardiac arrhythmias.
    - Risk factors for Torsade de Pointes such as hypokalemia, hypocalcemia and hypomagnesemia (unless corrected with adequate ongoing supplementation prior to and during study), cardiac failure, clinically significant/symptomatic bradycardia, or AV block > I.
    - Concomitant disease(s) that could prolong QT interval such as autonomic neuropathy (caused by diabetes, or Parkinson's disease), HIV, cirrhosis.
    - Concomitant medication(s) known to prolong the QT interval (see Appendix 1).
    - Any of the following within 6 months prior to starting study treatment: myocardial infarction (MI), angina pectoris, Coronary Artery Bypass Graft (CABG), Cerebrovascular Accident (CVA), Transient Ischemic Attack (TIA)
15. History of HIV infection, including a positive HIV test result (Elisa and Western blot). An HIV test is not required; however, previous medical history should be reviewed.
16. Screening ALT or AST > 2x ULN

[redacted]

17. Screening total bilirubin > 1.5x ULN
18. Renal dysfunction as defined by local metformin label (E.g., As per SmPC, creatinine clearance <60 mL/min; As per US package insert, serum creatinine >1.5 mg/dL (males), >1.4 mg/dL (females)) at screening.
19. Inadequate bone marrow function:
    - WBC < 2.5 x 10^9/L
    - Absolute Neutrophil Count (ANC) < 1.5 x 10^9/L
    - Platelets < 100 x 10^9/L
    - Hemoglobin < 9 g/dL
20. Abnormal coagulation function (PT and PTT elevated by 30% above normal limits, or INR ≥ 1.3 except for patients on anti-coagulant therapy. Patients on anticoagulant therapy must be stable for at least 1 month prior to study entry).
21. Any known contraindication to DPP-4 inhibitor, GLP-1 receptor agonists or insulin, including but not limited to:
    - Known family history of medullary thyroid cancer (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN2)
22. History of, or current alcohol misuse/abuse within the past 12 months.
23. Potentially unreliable or vulnerable individuals (e.g. person kept in detention) and those judged by the investigator to be unsuitable for the study are excluded from enrollment in the study.
24. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
25. 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 for 1 month following last dose of s.c. or 3 months following last dose of LAR formulation.
    Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. 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 patients on the study the vasectomized male partner should be the sole partner for that patient.

[redacted]

- 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.

26. Sexually active males unless they use a condom during intercourse while taking drug and for 1 month following last dose of s.c. or 3 months following last dose of LAR formulation 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.
27. Any current or prior medical condition (including clinically significant abnormal laboratory values) that can interfere with the conduct of the study or the evaluation of its results in the opinion of the investigator or the sponsor's medical monitor.

6 Treatment

6.1 Study treatment

Pasireotide

- Cushing's disease: Pasireotide (SOM230) s.c. injection: 300 - 900 µg b.i.d.; Starting dose = 600 µg b.i.d.
- Acromegaly: Pasireotide (SOM230) i.m. LAR: 20 – 60 mg every 28 days; Starting dose = 40 mg q28d

Anti-diabetic treatment

- 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
- Liraglutide administered s.c. once a day according to package insert
- Insulin administered s.c. according to package insert

[redacted]

6.1.1 Dosing regimen

Patients with Cushing's disease will receive pasireotide 600µg s.c. b.i.d. at study entry. Patients with acromegaly will receive pasireotide LAR 40 mg i.m. once/28days at study entry.

Table 6-1 Dose and treatment schedule

Treatment	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
Study drug			
Pasireotide s.c.	Subcutaneous injection	300 or 600 or 900 µg	Twice daily
Pasireotide LAR	Intramuscular injection	20 or 40 or 60 mg	Once/28 days
Anti-diabetic treatment			
Metformin	Oral	As per local package insert	Twice daily
Sitagliptin	Oral	50 or 100 mg based upon renal function	Once daily
Liraglutide	Subcutaneous injection	As per local package insert	Once daily
Insulin	Subcutaneous injection	investigator discretion	As per package insert

6.1.2 Rescue Therapy

For incretin-based therapy arm, rescue therapy will be instituted if the average of fasting SMBG values of 3 consecutive days is >160 mg/dL and FPG > 160 mg/dL by central lab during the randomized treatment period before dose stabilization for liraglutide is achieved. In addition, rescue therapy will be instituted if the average of fasting SMBG values of 3 consecutive days is ≥126 mg/dL and HbA1C > 7% by central lab after at least 6-week dose stabilization period with liraglutide is achieved. Patients receiving liraglutide in combination with or without metformin, with or without other OADs will be started on insulin. The dose of insulin and the type of insulin used (e.g. basal with or without prandial insulin) will be left to the discretion of the investigator. In addition, the decision to continue baseline therapy with either metformin and/or liraglutide will also be left to the investigator's discretion and the local prescribing guidelines.

6.1.3 Treatment duration

Pasireotide treatment duration in the core phase of the study will be:

- Up to 32 weeks for randomized patients (≤16 weeks pre-randomized period + 16 weeks post-randomization) dependent on when randomization occurs.
- 16 weeks for patients who do not randomize (observational arms).

Both the above group of patients will have the option to continue treatment on the extension phase of the study until the last patient randomized completes 16 weeks of treatment post-randomization, or when pasireotide is available commercially in their country or when a local access program is available.

Patients who will not continue pasireotide treatment (i.e. discontinued study treatment early in the core or extension phase, or complete core phase and do not move into the extension phase)

[redacted]

or patients who complete the extension phase will have a safety follow-up visit (779) 28 days after the last pasireotide s.c. dose or 84 days after the last pasireotide LAR dose.

Patients who are in the extension phase, who continue to receive clinical benefit as assessed by the investigator, will have the opportunity to receive pasireotide either commercially if available or via a roll-over study or local access program if available in order to continue their treatment with pasireotide.

For all patients, the EOP visit (778) will be performed. This includes patients who transition to commercial drug, the Safety follow-up visit (779) 28 days after the last pasireotide s.c. dose or 84 days after the last pasireotide LAR dose is required.

However, for patients who transition to a roll- over study or local access program, the Safety follow-up visit (779) 28 days after the last pasireotide s.c. dose or 84 days after the last pasireotide LAR dose is not required. Patients will continue to be monitored for safety while participating in either the roll-over study or local access program.

6.2 Dose modifications

6.2.1 Pasireotide dose modification

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. The following guidelines need to be applied:

After 8 weeks, Cushing's disease patients who experience a significant reduction in UFC levels as determined by site locally should continue to receive pasireotide at 600 µg s.c. b.i.d for as long as benefit is derived. A dose increase to 900 µg b.i.d after 8 weeks of treatment may be considered based on response to treatment, as long as the 600 µg b.i.d dose is well tolerated by the patient and glucose is controlled. Patients who have not responded to pasireotide after 8 weeks of treatment should be considered for discontinuation. At any time during the study the pasireotide dose may be reduced to 300 µg b.i.d for safety or tolerability reasons. Dose may be increased to 600 or 900 µg b.i.d if tolerability issues have resolved per investigator's discretion.

Dose up-titration of pasireotide LAR to 60 mg i.m. once/28 days after 12 weeks of treatment will be allowed in patients who do not achieve adequate levels of GH and IGF-1 (no reduction of mean GH level to <2.5 µg/L and no normalization of IGF-1 to within normal limits (age and sex related)) as determined locally. A dose reduction to 20 mg will be permitted in case of tolerability issues, but the patient may return to the 40 mg dose once tolerability issues are resolved.

Patients with an average fasting SMBG value of > 300 mg/dL for 3 consecutive days, who have been compliant with anti-diabetic medication and who do not have any co-morbidities influencing glucose metabolism, are to have a reduction of pasireotide dose. Dose reduction by decrements of 300 µg b.i.d for pasireotide s.c. and 20 mg/28days for pasireotide LAR is recommended. If the patients continue to have an average fasting SMBG values > 300 mg/dL for 3 consecutive days in spite of optimal anti-diabetic therapy, then pasireotide will be discontinued and a core EOP visit will be performed. The decision to discontinue is to be based on an assessment of risk and benefit by the investigator.

[redacted]

Dose should also be modified for adverse events that are suspected to be pasireotide-related as described in Table 6-2.

Any dose change must be recorded on the respective Dosage Administration Record CRF.

Table 6-2 Dose modification criteria for suspected pasireotide-related adverse events

Adverse event	Action
CTCAE grade ≤ 2	No drug adjustments
CTCAE grade ≥ 3 and assessed as study drug related	Reduce pasireotide to the next dose level. 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 again. The patient should stay on this lower dose and no further dose titrations are allowed. If the AE does not improve to grade ≤ 2, the dose is to be reduced further. 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.
For the management of hyperglycemia, QT prolongation, and LFT increases refer to specific instructions provided in Section 6.2.3.1, Section 6.2.3.2 and Section 6.2.3.3.	

6.2.2 Dose modification for anti-diabetic medications

Doses for anti-diabetic medications (metformin, sitagliptin, liraglutide) should be modified as per local prescribing label. Any dose change must be recorded on the respective Dosage Administration Record CRF during the core phase.

6.2.2.1 Metformin dose modification

If at any time during the study, the patient develops renal failure or renal dysfunction (creatinine clearance < 60 mL/min or as defined in the local label), metformin should be discontinued. Patient can continue on other allowed OADs based upon investigator judgment and in compliance with local prescribing guidelines. Patients in the pre-randomized period are eligible for randomization.

6.2.2.2 Sitagliptin dose modification

For patients with renal insufficiency sitagliptin dose should be modified as per local prescribing label.

Any dose change must be recorded on the respective Dosage Administration Record CRF during the core phase.

6.2.3 Follow-up for toxicities

6.2.3.1 Glucose monitoring

All patients need to be educated on the signs and symptoms of hyperglycemia and hypoglycemia. Patients must monitor their fasting blood glucose with a glucometer at home, and the blood glucose values will be captured in a diary. They should present the collected data to their study investigator for evaluation and for appropriate management during the core phase of the study. After their baseline visit, patients need to be instructed to call the site on a

[redacted]

weekly basis between visits during the core phase of the study for the investigator to review their SMBG values.

6.2.3.1.1 Hyperglycemia

The following process needs to be followed if the SMBG value is found to be elevated:

If the average fasting SMBG value is ≥ 126 mg/dL on 3 consecutive days:

During pre-randomized period

a. In anti-diabetic treatment naïve patients at study entry, patient need to be instructed to call the site to schedule a visit as soon as possible for parameters of glycemic control (FPG, HbA1C or random plasma glucose) at the central lab to confirm diabetes. If patients meet the criteria for diabetes, then anti-diabetic treatment should be initiated as soon as possible using metformin as described in Section 4.1.1.
b. Patients with the diagnosis of Type 2 diabetes entering the trial on the maximum tolerated dose of metformin OR metformin intolerant patients OR patients that have a contraindication for metformin OR patients being treated with other allowed OAD medications needs to be instructed to call the site to schedule a visit as soon as possible and be randomized immediately.
c. Patients with the diagnosis of Type 2 diabetes entering the trial on a sub-maximal dose of metformin need to have the dose of metformin titrated at weekly intervals to the maximal tolerated dose and follow the other steps as described in Section 4.1.1.

During randomized period

a. Patients on a stable dose of sitagliptin (adjusted for renal function) for at least 6 weeks, should stop sitagliptin and switched to liraglutide.
b. Patients past their 6-week dose stabilization period with liraglutide need to be instructed to call the site to schedule a visit as soon as possible for an HbA1c. If HbA1c>7%, then they should be started on rescue therapy with insulin. Please see Section 6.1.2 for details on rescue therapy. If patients are not on a stable dose of liraglutide for at least 6 weeks, then liraglutide dose should be adjusted according to the approved package insert.

If the average fasting SMBG value is >160 mg/dL on 3 consecutive days:

During pre-randomized period

a. In anti-diabetic treatment naïve patients at study entry, patients need to be instructed to call the site to schedule a visit as soon as possible for parameters of glycemic control (FPG, HbA1C or random plasma glucose) at the central lab to confirm diabetes. If patients meet the criteria for diabetes, then anti-diabetic treatment should be initiated using metformin as described in Section 4.1.1.

During randomized period

a. Patients on sitagliptin during the 6-week dose stabilization period need to be instructed to call the site to schedule a visit as soon as possible for a FPG level at the central lab. If the FPG>160 mg/dL then patients should be switched to liraglutide.

[redacted]

b. Patients on liraglutide (during or after the 6-week dose stabilization period) need to be instructed to call the site to schedule a visit as soon as possible for a FPG level at the central lab. If the FPG>160 mg/dL then patients should be started on rescue therapy with insulin. Please see Section 6.1.2 for details on rescue therapy.

If at any time the fasting SMBG is > 250 mg/dL:

a. Patients need to be instructed to call the site immediately for appropriate management of hyperglycemia. If the patients have an average fasting SMBG > 300 mg/dL on 3 consecutive days, they need to be instructed to return to the site as soon as possible for pasireotide dose reduction or study discontinuation (see Section 6.2.1).

6.2.3.1.2 Hypoglycemia

Hypoglycemia should be reported as an AE following the CTCAE version 4.03.

Patients who experience recurrent episodes of hypoglycemia in the absence of known precipitating factors may be eligible for dose reduction or adjustment in the dose of their anti-hyperglycemic therapy based on the investigator's clinical judgment.

Patients should not be discontinued from any treatment phase based on single episodes of hypoglycemia or symptoms of hypoglycemia unless clinically indicated.

6.2.3.2 QT-prolongation

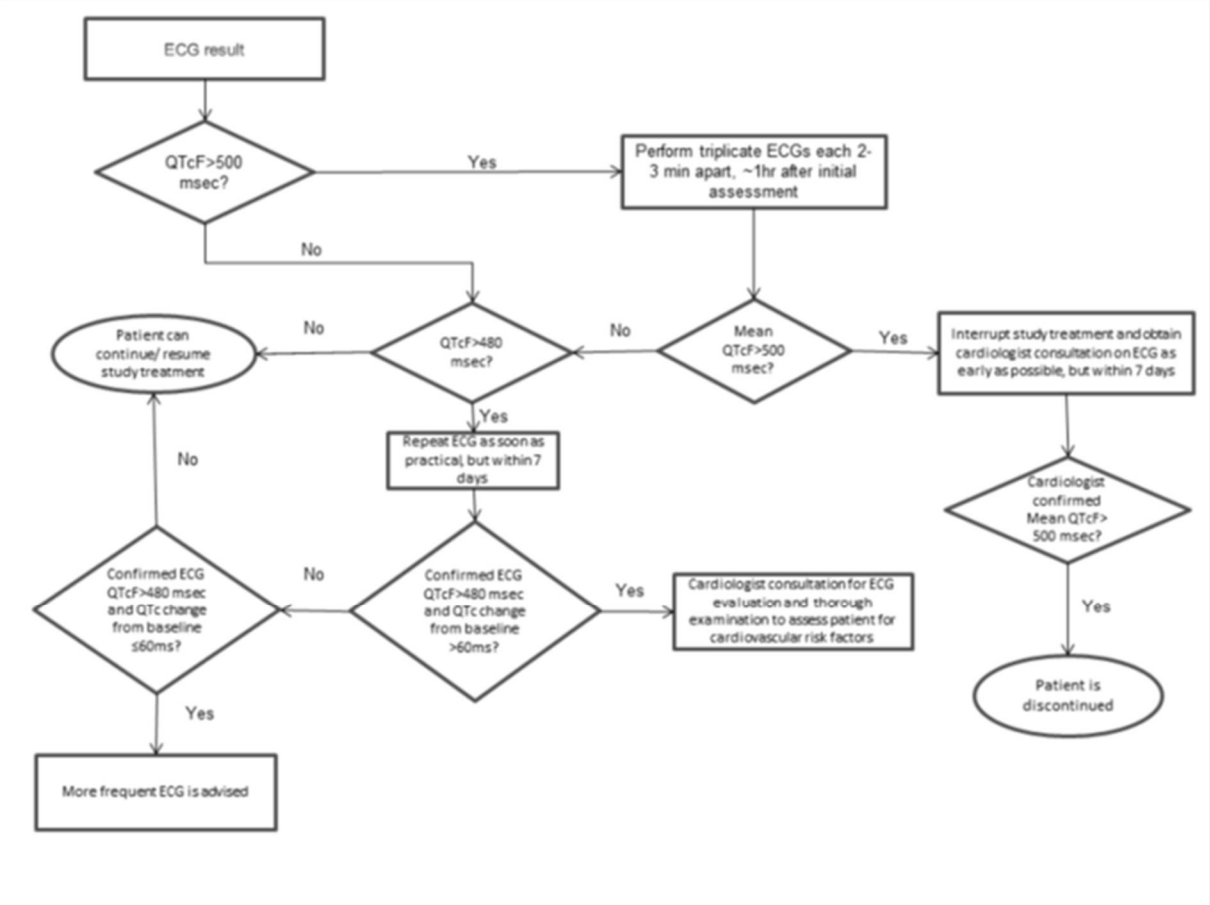
If at any visit QTcF > 500 ms is observed, triplicate ECGs, each 2-3 minutes apart, need to be collected approximately 1 hour after the initial ECG. The mean QTcF from the triplicate ECGs should be determined. If mean QTcF > 500 ms, study treatment should be interrupted until a cardiologist has re-evaluated the ECG (this can be done by the central cardiologist if the trial has one). Patient reassessment should be performed as early as possible but within 7 days of the initial abnormal ECG by a cardiologist for cardiovascular risk factors and a decision regarding study continuation.

If mean QTcF > 480 ms / ≤ 500 ms is observed, the repeat ECG assessment must be performed as soon as practical but within 7 days of the initial abnormal ECG. The following steps must be taken (Figure 6-1):

- If a QTcF > 480 ms / ≤ 500 ms is confirmed and QTcF change from pretreatment exceeds 60 ms, cardiology consultation must be sought as soon as practical (within 7 days) for ECG re-evaluation and clinical assessment for cardiovascular risk factors and a decision regarding study continuation.
- If a QTcF > 480 ms / ≤ 500 ms is confirmed and QTcF change from pretreatment < 60 ms, more frequent ECG follow-up is advised.

[redacted]

Figure 6-1 QT Prolongation Safety Management



6.2.3.3 Hepatic safety management

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

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

- ALT or AST > 3 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 including follow-up on potential Drug-induced Liver injury cases (DILI):

[redacted]

- 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, creatine kinase, PT (INR), ALP, and GGT. These tests should be monitored every **3-4 days** until resolution or return to baseline status.
- Perform hepatitis screen: anti-HAV, IgM (to confirm acute hepatitis A), HbsAg, Anti-HBc, anti-HCV (if positive, PCR viral load should be assessed), Anti-HEV, ANA antibodies, anti-smooth muscle anti-bodies, CMV and EBV
- Perform abdominal ultrasound (liver and biliary tree)

Patients should be managed according to the LFT algorithm Figure 6-2. Patients may need to be discontinued if the abnormal liver function criteria are met upon LFT retesting (see discontinuation criteria Section 7.1.3.1). Progress reports of the event should be maintained until resolution or stabilization (the latter defined as no further elevation after 2 consecutive assessments).

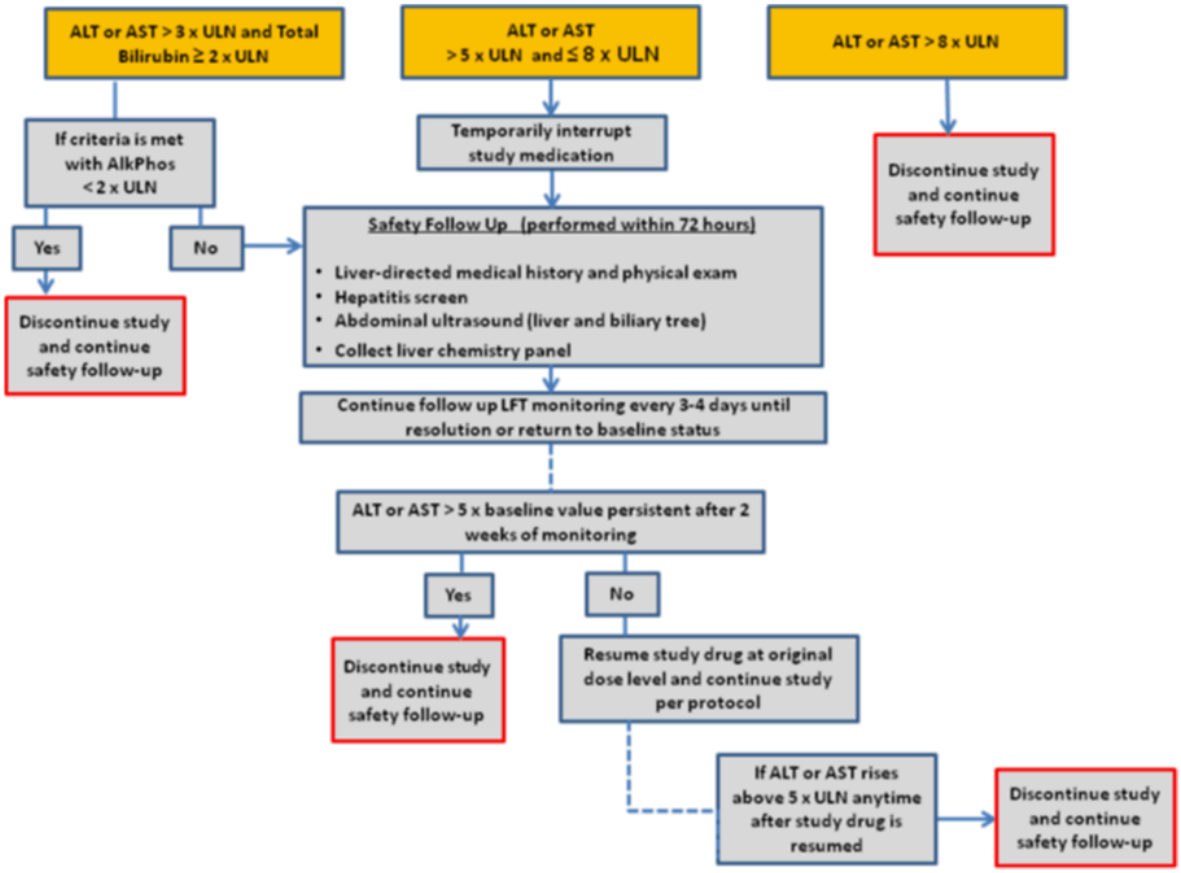
If any of these criteria are met and deemed an AE by the investigator, the event must be recorded on the Adverse Event eCRF page; if the event is deemed serious by the investigator, then the SAE form should be completed. In addition, any significant findings from the physical examination should be recorded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

For identification of potential Drug–induced Liver Injury (DILI), medical review by Novartis and the participating investigator needs to ensure that liver tests elevations are not caused by cholestasis, defined as ALP elevation >2.0 X ULN with R value (ALT/ALP in X ULN) <2. If confirmed, these patients should be immediately discontinued from the study drug treatment and repeat LFTs as soon as possible, preferably within 48 hours from the awareness of the abnormal results.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, without cholestasis, with no other alternative cause for LFT abnormalities identified should be considered as “medically significant”, thus, met the definition of SAE (Section 8.2.1) and reported as SAE using the term “potential Drug-induced Liver Injury”. All events should be followed up with the outcome clearly documented.

[redacted]

Figure 6-2 LFT management algorithm



6.2.4 Anticipated risks and safety concerns of the study drug

Appropriate eligibility criteria and specific Dose Limiting Toxicity (DLT) definitions, as well as specific dose modification and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced adverse events, i.e., hyperglycemia, QT prolongation and LFT increases are provided in Section 6.2.3. Refer to preclinical toxicity and or clinical data found in the [Investigator's Brochure].

6.3 Concomitant medications

6.3.1 Permitted concomitant therapy

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. 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 must be listed on the Concomitant medications/Significant non-drug therapies eCRF.

[redacted]

Any anti-diabetic medications that the patient takes during the study must be listed on the Concomitant medications/Significant non-drug therapies for Diabetes CRF. 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 one month after pasireotide s.c. last dose or for 3 months after pasireotide LAR last dose.

6.3.2 Permitted concomitant therapy requiring caution and/or action

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

6.3.3 Prohibited concomitant therapy

The use of concomitant medication known to prolong QT interval is prohibited. In case a patient needs to take QT prolonging drug, it will require study drug discontinuation prior to starting QT prolonging medication. Please see Appendix 1 for further guidance on QT prolonging medication.

The following washouts are to be followed prior to study entry (start of pasireotide) and the use of these drugs during the study is prohibited:

- All other medical therapies or other SSAs (octreotide, lanreotide) for Cushing's disease or acromegaly have to be discontinued at least 5 times the half-life of the respective preparation (8 weeks washout for octreotide LAR and lanreotide autogel)
- Dopamine agonists (bromocriptine, cabergoline) or pegvisomant (INN) will only be accepted provided the dose regimen is stable from at least 4 weeks before study entry and throughout the study.
- DPP-4 inhibitors or GLP-1 receptor agonists have to be discontinued for at least 4 weeks

6.4 Patient numbering, treatment assignment or randomization

6.4.1 Patient numbering

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

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

IRT must be notified within 2 days that the patient was not enrolled.

[redacted]

6.4.2 Treatment assignment or randomization

Patients will be assigned to either the incretin based therapy arm or the insulin arm in a 1:1 ratio if they meet the SMBG criteria during the pre-randomized period as specified in Section 4.1.1.

Randomization will be stratified by the following factors:

- Disease:
  a. Cushing's disease
  b. Acromegaly
- Glycemic status at baseline:
  a. HbA1c < 7 %
  b. HbA1c ≥ 7%

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the Interactive Response Technology (IRT) provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms.

All patients who fulfill randomization criteria will be randomized via IRT to one of the treatment arms. The investigator or his/her delegate will call or log on to the IRT and confirm that the patient fulfills all the randomization criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm. The randomization number will not be communicated to the caller.

6.4.3 Treatment blinding

Investigators, patients and the sponsor will have full knowledge of the treatment.

6.5 Study drug preparation and dispensation

Detailed instructions on the use of pasireotide solution for s.c. injection and pasireotide LAR for i.m. injection are provided in the pharmacy manual.

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

Pasireotide s.c will be provided as solution for injection in individual one-point-cut 1 mL ampule, containing 900, 600, and 300 µg pasireotide per 1 mL of solution.

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

[redacted]

6.5.1 Study drug packaging and labeling

Pasireotide s.c. will be provided in ampules and will be self-injected by the patients. Pasireotide LAR will be provided as powder for suspension in vials and solution for suspension ("vehicle") will be provided in ampules. Pasireotide LAR will be injected by a health care provider at the site.

The study medication packaging for globally supplied pasireotide has a 2-part label. Investigator staff will identify the study treatment package(s) to dispense to the patient. Investigator staff will add the patient number on the label. Immediately before dispensing the package, Investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique patient number. When medication is supplied locally, label will comply with local requirements.

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

Table 6-3 Packaging and labeling

Study treatments	Packaging	Labeling (and dosing frequency)
Pasireotide s.c.	Solution for subcutaneous injection in ampoule	Labeled as 'SOM230' (twice daily)
Pasireotide LAR	Microparticle powder for suspension in vial	Labeled as 'SOM230' LAR (once/28days)
	Solution for suspension (vehicle) in ampoule or pre-filled syringe	Labeled as 'solvent' (once/28days)

6.5.2 Drug supply and storage

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

Table 6-4 Supply and storage of study treatments

Study treatments	Supply	Storage
Pasireotide s.c.	Centrally or locally supplied by Novartis	Refer to study treatment label
Pasireotide LAR	Centrally or locally supplied by Novartis	Refer to study treatment label

6.5.3 Study drug compliance and accountability

6.5.3.1 Study drug compliance

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

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

6.5.3.2 Study drug accountability

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

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

6.5.3.3 Handling of other study treatment

The following anti-diabetic treatments have to be monitored specifically:

- Metformin
- Sitagliptin
- Liraglutide
- Insulin

Details are described in the monitoring plan.

All the above anti-diabetic medications will be supplied locally during the core phase of the study. These medications will not be provided by the sponsor during the extension phase of the study unless required by local regulations.

6.5.4 Disposal and destruction

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

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation.

No CRF will be used as a source document. The table indicates which assessments produce data to be entered into the database (D) or remain in source documents only (S) ("Category" column).

± 3-day visit window will be allowed for Cushing's patients. Visit windows for Acromegaly patients will remain unchanged as per Table 7-1.

Patients on pasireotide s.c. will have an additional visit at Week 1 (Visit 401) during pre-randomized period to perform liver function test and ECG monitoring. Patients on pasireotide

[redacted]

LAR will have an additional visit at Week 3 (Visit 402) during the pre-randomized period to perform ECG monitoring.

Patients who are not randomized by Week 16 (of pre-randomized period) will complete all assessments for Core EOP (Visit 777) on Week 16 (4 weeks from PR-W12).

Patients will complete all assessments for the randomization visit (Visit 7) on the day of randomization. After their randomization they will follow the visit schedule for randomized treatment period. Randomized patients will complete all assessments for Core EOP (Visit 777) approximately 16 weeks post-randomization.

During the course of the study:

- The dose of pasireotide (s.c or LAR) is to be administered after all assessments have been completed on the day of the visit.

[redacted]

Table 7-1 Core Phase Visit Evaluation Schedule

	Category	Protocol Section	Screening	Baseline	Pre-Randomized(PR) Period						Randomized(R) Treatment Period								Core EOP/ Early discontinuation	End of Study/ Follow-up
											Randomiza-tion									
Visit Number			**1**	**2**	**401**	**3**	**402**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**777**	**779**
Study Day			**-21 to -1**	**PR 1**	**PR 8**	**PR 15**	**PR 22**	**PR29**	**PR 57**	**PR 85**	**R 1**	**R15**	**R 29**	**R 43**	**R 57**	**R 71**	**R 85**	**R 99**		**28 days from last s.c dose/ 84 days from last LAR dose**
Study Week (W)				**PR-W0**	**PR-W1**	**PR-W2**	**PR-W3**	**PR-W4**	**PR-W8**	**PR-W12**	**R-W0**	**R-W2**	**R-W4**	**R-W6**	**R-W8**	**R-W10**	**R-W12**	**R-W14**	**PR-W16 / R-W16**	
Obtain Informed Consent	S	5.2	X																	
IWRS/IRT Registration	D	7.1.1.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Demography	D	7.1.1.3	X																	
Inclusion/exclusion criteria	D	5.2 / 5.3	X																	
Relevant medical history/current medical conditions	D	7.1.1.3	X																	

[redacted]

	Category	Protocol Section	Screening	Baseline	Pre-Randomized(PR) Period						Randomized(R) Treatment Period								Core EOP/ Early discontinuation	End of Study/ Follow-up
											Randomiza-tion									
Visit Number			**1**	**2**	**401**	**3**	**402**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**777**	**779**
Study Day			**-21 to -1**	**PR 1**	**PR 8**	**PR 15**	**PR 22**	**PR2 9**	**PR 57**	**PR 85**	**R 1**	**R1 5**	**R 29**	**R 43**	**R 57**	**R 71**	**R 85**	**R 99**		**28 days from last s.c dose/ 84 days from last LAR dose**
Study Week (W)				**PR - W0**	**PR-W1**	**PR-W2**	**PR-W3**	**PR-W4**	**PR - W8**	**PR-W12**	**R-W0**	**R-W2**	**R-W4**	**R-W6**	**R-W8**	**R-W10**	**R-W12**	**R-W14**	**PR-W16 / R-W16**	
Prior Diabetes History	D	7.1.1.3	X																	
Concomitant Medications	D	6.3	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	S	7.2.3.1	X	X				X	X	X	X		X		X		X		X	X
Height	D	7.2.3.3	X																	
Vital signs (Weight, Supine BP, Pulse, Temperature)	D	7.2.3.2	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X
HbA1c [Also to be collected prior to starting rescue therapy]	D	7.2.3.4.4	X	X				X	X	X	X		X		X		X		X	X

[redacted]

	Category	Protocol Section	Screening	Baseline	Pre-Randomized(PR) Period						Randomized(R) Treatment Period								Core EOP/ Early discontinuation	End of Study/ Follow-up
											Randomization									
Visit Number			**1**	**2**	**401**	**3**	**402**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**777**	**779**
Study Day			**-21 to -1**	**PR 1**	**PR 8**	**PR 15**	**PR 22**	**PR2 9**	**PR 57**	**PR 85**	**R 1**	**R1 5**	**R 29**	**R 43**	**R 57**	**R 71**	**R 85**	**R 99**		**28 days from last s.c dose/ 84 days from last LAR dose**
Study Week (W)				**PR - W0**	**PR-W1**	**PR-W2**	**PR-W3**	**PR-W4**	**PR - W8**	**PR-W12**	**R-W 0**	**R-W2**	**R-W 4**	**R-W 6**	**R-W8**	**R-W 10**	**R-W 12**	**R-W14**	**PR-W16 / R-W16**	
FPG [Also to be collected prior to starting rescue therapy]	D	7.2.3.4.4	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X
Fasting Insulin (Serum)	D	7.2.3.4.4		X							X		X		X		X		X	
Glucagon	D	7.2.3.4.4		X							X		X		X		X		X	
Self-monitored blood glucose (SMBG)	D	7.2.3.4.4			At Home Daily															
Hematology	D	7.2.3.4.1	X	X		X		X	X	X	X		X		X		X		X	X
Clinical Chemistry	D	7.2.3.4.2	X	X	X (s.c. only)	X		X	X	X	X		X		X		X		X	X

[redacted]

	Category	Protocol Section	Screening	Baseline	Pre-Randomized(PR) Period						Randomized(R) Treatment Period								Core EOP/ Early discontinuation	End of Study/ Follow-up
											Randomiza-tion									
Visit Number			**1**	**2**	**401**	**3**	**402**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**777**	**779**
Study Day			**-21 to -1**	**PR 1**	**PR 8**	**PR 15**	**PR 22**	**PR29**	**PR 57**	**PR 85**	**R 1**	**R15**	**R 29**	**R 43**	**R 57**	**R 71**	**R 85**	**R 99**		**28 days from last s.c dose/ 84 days from last LAR dose**
Study Week (W)				**PR-W0**	**PR-W1**	**PR-W2**	**PR-W3**	**PR-W4**	**PR-W8**	**PR-W12**	**R-W0**	**R-W2**	**R-W4**	**R-W6**	**R-W8**	**R-W10**	**R-W12**	**R-W14**	**PR-W16 / R-W16**	
Amylase and lipase	D	7.2.3.4.2	X	X		X		X	X	X	X		X		X		X		X	X
Urinalysis (Dipstick)	D	7.2.3.4.3	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation	D	7.2.3.4.5	X	X				X			X		X		X		X		X	
Hepatitis B and C tests	D	7.2.3.4.8	X																	
Serum Pregnancy test	D	7.2.3.4.10	X																	
Urine Pregnancy test	D	7.2.3.4.10		X				X			X		X		X		X		X	X
Free T4, TSH	D	7.2.3.4.6	X	X															X	
GLP-1, GIP	D	7.2.3.4.7		X							X				X				X	
GH, IGF-1	D	7.2.3.4.7		X							X				X				X	
Serum Cortisol	D	7.2.3.4.7		X							X				X				X	
Plasma ACTH	D	7.2.3.4.7		X							X				X				X	

[redacted]

	Category	Protocol Section	Screening	Baseline	Pre-Randomized(PR) Period						Randomized(R) Treatment Period								Core EOP/ Early discontinuation	End of Study/ Follow-up
											Randomiza-tion									
Visit Number			**1**	**2**	**401**	**3**	**402**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**777**	**779**
Study Day			**-21 to -1**	**PR 1**	**PR 8**	**PR 15**	**PR 22**	**PR2 9**	**PR 57**	**PR 85**	**R 1**	**R1 5**	**R 29**	**R 43**	**R 57**	**R 71**	**R 85**	**R 99**		**28 days from last s.c dose/ 84 days from last LAR dose**
Study Week (W)				**PR - W0**	**PR-W1**	**PR-W2**	**PR-W3**	**PR-W4**	**PR - W8**	**PR-W12**	**R-W0**	**R-W2**	**R-W4**	**R-W6**	**R-W8**	**R-W10**	**R-W12**	**R-W14**	**PR-W16 / R-W16**	
ECG (12 lead)	D	7.2.3.6.1	X	X	X (s.c. only)		X (LAR only)				X		X		X		X		X	
Gall-bladder Ultrasound	D	7.2.3.5	X																X	
Adverse Events	D	8.1			Continuous															
Study Drug (pasireotide s.c.) administration record for patients with Cushing's disease (daily b.i.d dosing) [Last dose is one day prior to Core EOP visit]	D	6.1		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

[redacted]

	Category	Protocol Section	Screening	Baseline	Pre-Randomized(PR) Period						Randomized(R) Treatment Period								Core EOP/ Early discontinuation	End of Study/ Follow-up
											Randomization									
Visit Number			**1**	**2**	**401**	**3**	**402**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**777**	**779**
Study Day			**-21 to -1**	**PR 1**	**PR 8**	**PR 15**	**PR 22**	**PR2 9**	**PR 57**	**PR 85**	**R 1**	**R15**	**R 29**	**R 43**	**R 57**	**R 71**	**R 85**	**R 99**		**28 days from last s.c dose/ 84 days from last LAR dose**
Study Week (W)				**PR - W0**	**PR-W1**	**PR-W2**	**PR-W3**	**PR-W4**	**PR - W8**	**PR-W12**	**R-W0**	**R-W2**	**R-W4**	**R-W6**	**R-W8**	**R-W10**	**R-W12**	**R-W14**	**PR-W16 / R-W16**	
Study Drug (pasireotide LAR) administration for patients with acromegaly (once/28 days) [Last dose is 1 month prior to core EOP visit]	D	6.1		X				X	X	X	X (administer every 3-4 weeks from prior dose)									
Anti-Diabetic Drug Administration Record	D	4.1		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Phase Completion	D	7.1.3																	X	
Study Completion	D	7.1.4																		X

[redacted]

Table 7-2 Extension Phase Visit Evaluation Schedule

	Category	Protocol Section	Start of Extension	Annual Visits during Extension(E)														Extension EOP	End of Study/ Follow-up
Visit Number			**15**	**16/ 30/..**	**17/ 31/..**	**18/ 32/..**	**19/ 33/..**	**20/ 34/..**	**21/ 35/..**	**22/ 36/..**	**23/ 37/..**	**24/ 38/..**	**25/ 39/..**	**26/ 40/..**	**27/ 41/..**	**28/ 42/..**	**29/ 43/..**	**77 8**	**779**
Study Day			**E1**	**E29/ 421/..**	**E57/ 449/..**	**E85/ 477/..**	**E113 / 505/..**	**E141 / 533/..**	**E169 / 561/..**	**E197 / 589/..**	**E225 / 617/..**	**E253/ E645/..**	**E281 / 673/..**	**E309 / 701/..**	**E337 / 729/..**	**E365 / 757/..**	**E393 / 785/..**		**28 days from last s.c dose/ 84 days from last LAR dose**
Study Week (W)			**EW 0**	**EW4 / 60/..**	**EW 8/ 64/..**	**EW 12/ 68/..**	**EW 16/ 72/..**	**EW 20/ 76/..**	**EW 24/ 80/..**	**EW 28/ 84/..**	**EW 32/ 88/..**	**EW 36/ 92/..**	**EW 40/ 96/..**	**EW 44/ 100/..**	**EW 48/ 104/..**	**EW 52/ 108/..**	**EW 56/ 112/..**		
IWRS/IRT Registration	D	7.1.1.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications	D	6.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	S	7.2.3.1			X		X		X		X		X		X		X	X	X
Vital signs (Weight, Supine BP, Pulse, Temperature)	D	7.2.3.2 7.2.3.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HbA1c	D	7.2.3.4.4			X		X		X		X		X		X		X	X	X

[redacted]

	Category	Protocol Section	Start of Extension	Annual Visits during Extension(E)														Extension EOP	End of Study/ Follow-up
Visit Number			**15**	**16/ 30/..**	**17/ 31/..**	**18/ 32/..**	**19/ 33/..**	**20/ 34/..**	**21/ 35/..**	**22/ 36/..**	**23/ 37/..**	**24/ 38/..**	**25/ 39/..**	**26/ 40/..**	**27/ 41/..**	**28/ 42/..**	**29/ 43/..**	**77 8**	**779**
Study Day			**E1**	**E29/ 421/..**	**E57/ 449/..**	**E85/ 477/..**	**E113 / 505/..**	**E141 / 533/..**	**E169 / 561/..**	**E197 / 589/..**	**E225 / 617/..**	**E253/ E645/..**	**E281 / 673/..**	**E309 / 701/..**	**E337 / 729/..**	**E365 / 757/..**	**E393 / 785/..**		**28 days from last s.c dose/ 84 days from last LAR dose**
Study Week (W)			**EW 0**	**EW4 / 60/..**	**EW 8/ 64/..**	**EW 12/ 68/..**	**EW 16/ 72/..**	**EW 20/ 76/..**	**EW 24/ 80/..**	**EW 28/ 84/..**	**EW 32/ 88/..**	**EW 36/ 92/..**	**EW 40/ 96/..**	**EW 44/ 100/..**	**EW 48/ 104/..**	**EW 52/ 108/..**	**EW 56/ 112/..**		
FPG	D	7.2.3.4.4		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	D	7.2.3.4.1			X		X		X		X		X		X		X	X	X
Clinical Chemistry	D	7.2.3.4.2			X		X		X		X		X		X		X	X	X
Urinalysis (dipstick)	D	7.2.3.4.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test	D	7.2.3.4.10							X						X			X	X
Gall-bladder Ultrasound	D	7.2.3.5														X			
Adverse Events	D	8.1		Continuous															

[redacted]

	Category	Protocol Section	Start of Extension	Annual Visits during Extension(E)														Extension EOP	End of Study/ Follow-up
Visit Number			**15**	**16/ 30/..**	**17/ 31/..**	**18/ 32/..**	**19/ 33/..**	**20/ 34/..**	**21/ 35/..**	**22/ 36/..**	**23/ 37/..**	**24/ 38/..**	**25/ 39/..**	**26/ 40/..**	**27/ 41/..**	**28/ 42/..**	**29/ 43/..**	**77 8**	**779**
Study Day			**E1**	**E29/ 421/..**	**E57/ 449/..**	**E85/ 477/..**	**E113 / 505/..**	**E141 / 533/..**	**E169 / 561/..**	**E197 / 589/..**	**E225 / 617/..**	**E253/ E645/..**	**E281 / 673/..**	**E309 / 701/..**	**E337 / 729/..**	**E365 / 757/..**	**E393 / 785/..**		**28 days from last s.c dose/ 84 days from last LAR dose**
Study Week (W)			**EW 0**	**EW4 / 60/..**	**EW 8/ 64/..**	**EW 12/ 68/..**	**EW 16/ 72/..**	**EW 20/ 76/..**	**EW 24/ 80/..**	**EW 28/ 84/..**	**EW 32/ 88/..**	**EW 36/ 92/..**	**EW 40/ 96/..**	**EW 44/ 100/..**	**EW 48/ 104/..**	**EW 52/ 108/..**	**EW 56/ 112/..**		
Study Drug (pasireotide s.c.) administration record for patients with Cushing's disease (daily b.i.d dosing)	D	6.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

[redacted]

	Category	Protocol Section	Start of Extension	Annual Visits during Extension(E)														Extension EOP	End of Study/ Follow-up
Visit Number			**15**	**16/ 30/..**	**17/ 31/..**	**18/ 32/..**	**19/ 33/..**	**20/ 34/..**	**21/ 35/..**	**22/ 36/..**	**23/ 37/..**	**24/ 38/..**	**25/ 39/..**	**26/ 40/..**	**27/ 41/..**	**28/ 42/..**	**29/ 43/..**	**77 8**	**779**
Study Day			**E1**	**E29/ 421/..**	**E57/ 449/..**	**E85/ 477/..**	**E113 / 505/..**	**E141 / 533/..**	**E169 / 561/..**	**E197 / 589/..**	**E225 / 617/..**	**E253/ E645/..**	**E281 / 673/..**	**E309 / 701/..**	**E337 / 729/..**	**E365 / 757/..**	**E393 / 785/..**		**28 days from last s.c dose/ 84 days from last LAR dose**
Study Week (W)			**EW 0**	**EW4 / 60/..**	**EW 8/ 64/..**	**EW 12/ 68/..**	**EW 16/ 72/..**	**EW 20/ 76/..**	**EW 24/ 80/..**	**EW 28/ 84/..**	**EW 32/ 88/..**	**EW 36/ 92/..**	**EW 40/ 96/..**	**EW 44/ 100/..**	**EW 48/ 104/..**	**EW 52/ 108/..**	**EW 56/ 112/..**		
Study Drug (pasireotide LAR) administration for patients with acromegaly (once/28 days)	D	6.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Study Phase Completion	D	7.1.3																X	
Study Completion	D	7.1.4																	X

[redacted]

7.1.1 Screening

The informed consent form must be signed prior to ANY screening procedure being performed. Once the patient has consented to participate in the study he/she will be screened for eligibility at Visit 1. Informed consent must be signed and dated prior to any study related procedure at Visit 1. During the screening period the inclusion and exclusion criteria will be assessed. The screening period for this study is a maximum of 21 days (3 weeks) to allow sufficient time for laboratory and procedural assessments prior to study drug administration. Patients that do not meet eligibility criteria are allowed to be rescreened once more and should keep the same patient ID number. The rescreening should be documented in the source files. All assessments are to be repeated when patients are rescreened.

7.1.1.1 Eligibility screening

Following registration in IRT for screening, patient eligibility will be checked once all screening procedures are completed. The eligibility check will be embedded in IRT system. Please refer and comply with detailed guidelines in the IRT manual.

7.1.1.2 Information to be collected on screening failures

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the Screening Log Page. The demographic information must be completed for Screen failure patients. No other data will be entered into the clinical database for patients who are screen failures.

7.1.1.3 Patient demographics and other baseline characteristics

Standard demographic information and medical history will be collected. Diabetes history together with the medication/treatment used will also be collected. Other baseline assessments will be collected as per Table 7-1.

7.1.2 Treatment period

The treatment period in the core phase of the study will be up to 32 weeks. Patients that are randomized within 16 weeks of study entry will continue in the core phase for 16 weeks post-randomization. Patients that are not randomized complete their core phase at pre-randomized period Week 16 (PR-W16). Both group of patients will have the option to continue pasireotide treatment in the extension phase of the study until the last patient randomized completes 16 weeks of treatment post-randomization, or when pasireotide is available commercially or when a local access program is available.

Pre-randomized period

The pre-randomized period can be up to 16 weeks. Eligible patients will start pasireotide s.c. for Cushing's disease and pasireotide LAR for acromegaly. If they experience increases in their fasting blood glucose, they will start anti-diabetic treatment using metformin. If they continue to experience increases in their fasting blood glucose within the first 16 weeks, they

[redacted]

will be randomized. During the pre-randomized period, patients will have visits every two weeks in the first month and then monthly visits (see Table 7-1).

Randomized period

Patients are randomized in a 1:1 ratio to receive treatment with incretin based therapy (sitagliptin followed by liraglutide) or insulin for approximately 16 weeks. During the randomized period, patients will have visits every two weeks (see Table 7-1).

7.1.3 End of treatment visit including study completion and premature withdrawal

Patients who discontinue study treatment before visit 777 (if patient is in the core phase of the study) or 778 (if patient is in the extension phase of the study), should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the Core EOP or Extension EOP visit will be performed (Table 7-1 and Table 7-2). A Study Phase Completion CRF page should be completed, giving the date and reason for stopping the study treatment. These patients should then return for an End of Study/Follow-up visit as described in Section 7.1.4 and complete the EOS Visit assessments and Study Completion eCRF. Patients continuing pasireotide treatment through a roll-over study or local access program will not return for an End of Study/Follow-up visit as their safety will be monitored.

At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations either 28 days following the last dose of s.c treatment for Cushing's patients or 84 days following the last dose of LAR treatment for acromegaly patients.

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

If a study withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the Study Phase Completion CRF page and Study Completion CRF page.

If a patient discontinues study treatment, but continues on to the end of treatment and final end of study assessments, the patient remains on study until such time as he/she completes protocol criteria for ending study assessments. At that time, the reason for study completion should be recorded on the Study Completion CRF page.

If using IRT, the Investigator must contact the IRT to register the patient's discontinuation.

End of phase/Premature withdrawal visit is not considered as the end of the study.

7.1.3.1 Criteria for premature patient withdrawal

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

[redacted]

- Adverse event(s)[including abnormal laboratory values(s) and abnormal test procedures results(s)]
- Patient withdrew consent
- Lost to follow-up
- Death
- Pregnancy

In addition to the general withdrawal criteria, the study specific criteria below also require immediate study drug discontinuation. Proper safety follow-up management should be performed as outlined in Section 6.2.3.1, Section 6.2.3.2 and Section 6.2.3.3. Re-challenge of study medication is prohibited once discontinuation criteria are met.

Hepatic-related discontinuation criteria

- Jaundice or other signs of clinically significant liver dysfunction
- ALT or AST > 3 x ULN and Total Bilirubin ≥ 2 x ULN and ALP < 2 x ULN
- ALT or AST > 5 x ULN and ≤ 8 x ULN persistent for more than 2 weeks
- ALT or AST > 8 x ULN

Following discontinuation of treatment with pasireotide, patients should be monitored until resolution. Treatment should not be restarted.

QT related discontinuation criteria

- Confirmed QTcF > 500 ms and discontinuation recommended by a cardiologist
- Clinically significant arrhythmias including:
  1. Any ventricular or supra-ventricular tachyarrhythmia associated with symptoms of hemodynamic compromise.
  2. Sustained ventricular tachycardia (VT > 30 s) irrespective of symptoms.
  3. Recurrent non-sustained VT (≥ 3 beats) during any 24-hour monitoring period.
  4. Clinically significant brady-arrhythmia or third degree AV block.
  5. Need to use QT prolonging medication.

Hyperglycemia related discontinuation criteria

- Uncontrolled diabetes mellitus (DM), consistently high glucose values with average of fasting SMBG values of 3 consecutive days > 300 mg/dL or HbA1c value ≥ 10 % despite prior appropriate anti-diabetic management and prior dose adjustment of the pasireotide.

Pancreas-related discontinuation criteria

If clinical diagnosis of pancreatitis is suspected, as per investigator's discretion, then patient should be discontinued from the study.

The investigator must also notify the IRT of the premature withdrawal, if this occurs during the core period.

[redacted]

7.1.4 Follow-up and End of Study visit

All patients must have safety evaluations and complete the EOS assessments at the EOS visit 28 days after the last dose of pasireotide s.c or 84 days after the last dose of pasireotide LAR. Patients continuing pasireotide treatment through a roll-over study or local access program will not return for an End of Study/Follow-up visit as their safety will be monitored.

Refer to the eCRF Completion Guidelines for further instructions.

Patients lost to follow up should be recorded as such on the CRF. For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc. Patients that meet the requirements for follow up of abnormal LFTs at the end of study visit should be followed up as detailed in Section 6.2.3.3.

7.2 Assessment types

7.2.1 Efficacy assessments

There are no efficacy assessments for pasireotide in this study. Clinical benefit with pasireotide should be evaluated as described in Section 7.2.2.

Change in HbA1c from the time of randomization to approximately 16 weeks post-randomization between incretin based therapy arm and insulin arm will be assessed to determine the efficacy of anti-diabetic therapy on pasireotide-induced hyperglycemia. Change in HbA1c and FPG from baseline to Core EOP in patients who received pasireotide by treatment group will also be assessed. Please see Section 7.2.3.4.4 for details.

7.2.2 Clinical benefit assessments

Clinical benefit should be evaluated 8 weeks after the start of pasireotide s.c. and 12 weeks after the start of pasireotide LAR to determine if pasireotide dose modification is needed. Please refer to Section 6.2.1. Clinical benefit can also be evaluated any time afterwards at investigator's discretion.

mUFC levels for patients with Cushing's disease and GH and IGF-1 levels for patients with acromegaly should be determined by site locally. These evaluations should be part of the source documentation at the site.

7.2.3 Safety and tolerability assessments

Safety will be monitored by assessing laboratory assessments, ECGs, imaging for gallstones, vital signs and physical examinations as well as collecting of adverse events at every visit. For details on AE collection and reporting, refer to Section 8.1.

7.2.3.1 Physical examination

A complete physical exam must be performed by the investigator at visits indicated below and in Table 7-1 and Table 7-2. These examinations will be performed according to the standards at each institution.

[redacted]

Physical Examinations will be performed on the scheduled visits. More frequent examinations may be performed at the investigator's discretion, if medically indicated. The physical examination comprises a total body examination (general appearance, skin, neck, including thyroid, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities and nervous system).

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

7.2.3.2 Vital signs

Vital signs (supine blood pressure, pulse rate and body temperature) will be performed by the investigator at all visits as indicated in Table 7-1 and Table 7-2 and recorded in the appropriate eCRFs. More frequent examinations may be performed at the investigator's discretion, if medically indicated.

7.2.3.3 Height and weight

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

- Height will be measured at screening only
- Weight will be measured at every visit during the core and extension phase of the study

7.2.3.4 Laboratory evaluations

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

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

[redacted]

Table 7-3 Central Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	RBC, Hematocrit, Hemoglobin, MCH, MCHC, MCV, Platelets, WBC including Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)
Clinical Chemistry	Albumin, Total Protein, Alkaline phosphatase, GGT, ALT, AST, Total Bilirubin, direct Bilirubin, indirect Bilirubin, Bicarbonate, Sodium, Potassium, Calcium, Chloride, Creatine kinase, Total Cholesterol, LDL, HDL, Triglycerides, Creatinine, Blood Urea Nitrogen (BUN) or Urea, Uric Acid
Hyperglycemia related tests	HbA1c, fasting plasma glucose, fasting insulin, glucagon
Coagulation	Prothrombin time (PT), International normalized ratio (INR), Activated partial thromboplastin time (APTT)
Thyroid	Free T4, TSH
Additional tests	IGF-1, GH, GLP-1, GIP, serum cortisol, plasma ACTH. Screening only: Serum pregnancy test, Hepatitis B and C tests (HbsAg, anti-HCV). Hepatic safety follow-up: Hepatitis A (anti-HAV, IgM), Anti-HBc, anti-HCV (if positive, PCR viral load will be assessed), Anti-HEV, ANA antibodies, anti-smooth muscle anti-bodies, CMV and EBV Pancreatic safety: Lipase and Amylase

7.2.3.4.1 Hematology

Hemoglobin, hematocrit, WBC with differential, RBC, MCV, MCH, MCHC and platelet count will be measured at visits indicated in Table 7-1 and Table 7-2.

7.2.3.4.2 Clinical chemistry

Albumin, total protein, alkaline phosphatase, GGT, ALT (GPT), AST (GOT), total bilirubin, direct bilirubin, indirect bilirubin, bicarbonate, sodium, potassium, calcium, chloride, Creatine Kinase, total cholesterol, LDL, HDL, Triglycerides, Creatinine, Blood Urea Nitrogen (BUN) or Urea, Uric Acid will be measured at visits indicated in Table 7-1 and Table 7-2.

Investigator should calculate creatinine clearance at each visit to assess if dose modification or discontinuation is required for pasireotide and/or anti-diabetic medications. (Please see Section 6.2.2.1 and Section 6.2.2.2) Creatinine clearance calculation will be recorded in the source document and will not be captured in the eCRF.

7.2.3.4.3 Urinalysis

Urinalysis includes dipstick analysis (glucose, bilirubin, ketone, specific gravity, blood, pH, protein and leukocyte esterase). Urinalysis will be analyzed locally at visits indicated in Table 7-1 and Table 7-2.

7.2.3.4.4 Hyperglycemia related tests

HbA1c, fasting plasma glucose, fasting insulin and glucagon will be measured at visits indicated in Table 7-1 and Table 7-2.

FPG and/or HbA1c will also be measured at unscheduled visits for the following reasons:

[redacted]

- To confirm diagnosis of diabetes in anti-diabetic treatment naïve patients prior to initiating anti-diabetic treatment.
- To confirm an FPG > 160 mg/dl during the 6-week dose stabilization period prior to switching from sitagliptin to liraglutide
- To confirm an FPG > 160 mg/dl during the 6-week dose stabilization period prior to switching from liraglutide to rescue therapy.
- To confirm an HbA1c > 7% in patients after the 6-week dose stabilization period on liraglutide prior to starting rescue therapy.

FPG and HbA1c should be measured prior to starting rescue therapy as well.

Please refer to Section 4.1 for guidance on anti-diabetic treatment management.

Self-monitored blood glucose

All patients will measure their fasting blood glucose with a glucometer at home daily after study enrollment. The patients will be instructed to record the glucose values in their glycemia diary. At each scheduled visit, the study investigator will review the patient's fasting self-monitored blood glucose (SMBG) values. After their baseline visit, patients will also be instructed to call the site on a weekly basis between visits during the core phase of the study for the investigator to review their SMBG values. Highest and lowest SMBG values since the last visit and the last 3 fasting SMBG values prior to the visit will be recorded in the eCRF.

7.2.3.4.5 Coagulation

Prothrombin time (PT), International normalized ratio (INR), and activated partial thromboplastin time (APTT) will be performed at visits indicated in Table 7-1 and Table 7-2.

7.2.3.4.6 Thyroid

Free T4 and TSH will be measured at visits indicated in Table 7-1 and Table 7-2.

7.2.3.4.7 Hormones

IGF-1, GH, GLP-1, GIP, serum cortisol and plasma ACTH will be measured at visits indicated in Table 7-1 and Table 7-2.

7.2.3.4.8 Liver function testing

Presence of HbsAg and Anti-HCV are to be assessed during screening.

If at any visit abnormal liver function criteria as described in Section 6.2.3.3 are met, a hepatic safety follow-up as described in Section 6.2.3.3 should be performed immediately within 72 hours of awareness of the abnormality.

7.2.3.4.9 Pancreas function testing

Serum lipase and amylase will be measured at visits indicated in Table 7-1 and Table 7-2.

[redacted]

7.2.3.4.10 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have a serum B-hCG pregnancy test at screening visit and urine pregnancy test at visits indicated in Table 7-1 and Table 7-2. A positive pregnancy test requires immediate interruption of study treatment until the assessment is confirmed. If positive, the patient must be discontinued from the study.

7.2.3.5 Gallbladder ultrasound

A gallbladder ultrasound will be performed at the sites at screening visit, and core EOP visit (777). Additionally, a gallbladder ultrasound will be performed every 12 months during the Extension Phase. The results will be recorded in the eCRF.

7.2.3.6 Cardiac assessments

7.2.3.6.1 Electrocardiogram (ECG)

Standard 12 lead ECGs will be performed locally at the sites at visits during the core phase as indicated in Table 7-1 and Table 7-4. If the ECG machine at your site does not automatically provide QTcF then use the formula in Appendix 2 to calculate it.

If at any visit QTcF >500 ms is observed, all the procedures for QT-prolongation described in Section 6.2.3.2 should be followed.

ECGs will be obtained after the patient has been supine and resting for at least 10 minutes prior to each time point indicated. All ECGs should be recorded with the patient in the same physical position.

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

Table 7-4 Local ECG collection plan

CORE			
Week	**Day**	**Time**	**ECG Type**
CORE PHASE:			
Screening	-21 to -1	Anytime	12 lead
PR-W0	PR1	Pre-dose	12 Lead
PR-W1 (pasireotide s.c. only)	PR8	Pre-dose	12 Lead
PR-W3 (pasireotide LAR only)	PR22	Pre-dose	12 Lead
R-W0	R1	Pre-dose	12 Lead
R-W4	R29	Pre-dose	12 Lead
R-W8	R57	Pre-dose	12 Lead
R-W12	R85	Pre-dose	12 Lead
Core EOP		Anytime	12 Lead
Unscheduled sample		Anytime	12 Lead

7.2.3.7 Tolerability

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

7.2.3.8 Other assessments

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

7.2.4 Resource utilization

Not applicable.

7.2.5 Patient reported outcomes

Not applicable.

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

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

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

[redacted]

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF. Adverse event monitoring should be continued for at least 28 days after the last pasireotide s.c. dose or 84 days after the last pasireotide LAR dose. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

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

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

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

1. The severity grade (CTCAE Grade 1-4)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes, investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

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

[redacted]

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an adverse event in their own right (CTCAE grade ≥3; are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

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

8.1.3 Adverse events of special interest

Based on the knowledge of the SSA drug class and experience gained during the clinical development of pasireotide, two areas of risks associated with pasireotide treatment have been identified: risks which are known SSA class effects, and risks which were observed mainly in pre-clinical studies. The risks identified as class effects of SSAs are the following: QT-prolongation, bradycardia, hyperglycemia, cholelithiasis, hematological abnormalities, abnormal liver functions, injection site reactions, gastrointestinal disorders, pancreatitis, and hypothyroidism. Risks which were mainly seen in pre-clinical studies are coagulation abnormalities, hypotension, hypocalcaemia, and gastrointestinal erosions/bleedings. In addition, hypocortisolism/cortisol withdrawal syndrome is an identified risk for patients with Cushing's disease treated with pasireotide.

Based on these identified risks, several categories of AEs of special interest were defined. These categories consist of AEs where pasireotide may influence a common mechanism of action responsible for triggering them, or that are similar in nature (although not identical).

8.1.3.1 Definitions and reporting

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

[redacted]

8.2 Serious adverse events

8.2.1 Definitions

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

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

8.2.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 1 month for those patients who discontinued pasireotide s.c and at least 84 days for those patients who discontinued pasireotide LAR must be reported to Novartis within 24 hour of learning of its occurrence.

Any SAEs experienced after this 28 days period for pasireotide s.c. and 84 days for pasireotide LAR (or 5 half-lives, whichever is longer) should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the oncology Novartis Drug Safety and Epidemiology (DS&E) department.

[redacted]

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

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

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

8.3 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

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

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Newborn of a patient (or a partner of a patient) who becomes pregnant during the study within 1 month of the last pasireotide s.c. dose (or within 3 months of the last pasireotide LAR dose) should be followed for 3 months post-delivery (from Day 0 to Month 3 of life).

8.4 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided [Investigator Brochure]. Additional safety information collected between IB updates will be communicated

[redacted]

in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.5 Steering Committee

The steering committee (SC) will be established comprising investigators participating in the trial, i.e. not being members of the DMC (Data Monitoring Committee) and Novartis representatives from the Clinical Trial Team.

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

8.6 Data Monitoring Committee

There is no DMC for the study.

9 Data collection and management

9.1 Data confidentiality

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

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

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

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

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the

completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

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

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

9.3 Data collection

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

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

9.4 Database management and quality control

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

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

Samples and/or data will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all study treatments dispensed to the patient and all IRT assigned dosage changes will be tracked using an Interactive Response Technology. The

system will be supplied by a vendor(s), who will also manage the database. The data will be sent electronically to Novartis personnel (or designated CRO).

At the conclusion of the study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis personnel (or designated CRO). The occurrence of any protocol violations will be determined. After these actions have been completed and the data has been verified to be complete and accurate, the database will be declared locked and the treatment codes will be unblinded and made available for data analysis. Authorization is required prior to making any database changes to locked data, by joint written agreement between the Global Head of Biostatistics and Data Management and the Global Head of Clinical Development.

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

10 Statistical methods and data analysis

The study will be analyzed when all treated patients have completed or discontinued the study and the final CSR will be produced. Additional interim CSR may be performed at the end of the core phase as needed.

Novartis or designated CRO will analyze all data using the SAS System for data analysis V8.0 or higher. 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.

10.1 Analysis sets

10.1.1 Randomized Analysis Set

The Randomized Analysis Set (RAS) comprises all patients who received at least one dose of pasireotide and have been assigned to either incretin based therapy or insulin by randomization. According to the ITT principle, patients will be analyzed according to the treatment they have been assigned to during the randomization procedure. RAS will be used for the primary analysis and some secondary analyses.

10.1.2 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients who receive at least one dose of pasireotide. The anti-diabetic treatment group will follow the Intent-To-Treat (ITT) principle.

[redacted]

10.1.3 Safety analysis Set

The Safety Analysis Set (SAS) includes all patients who received at least one dose of pasireotide and had at least one post-baseline safety assessment. SAS will be used for safety summaries. Randomized patients within SAS will be analyzed according to the anti-diabetic study treatment first received.

Please note: the statement that a patient had no adverse events (on the Adverse Event CRF) constitutes a safety assessment. Patients who have received at least one dose of study drug but who have no post-treatment safety data of any kind would be excluded from the SAS.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data will be summarized descriptively for the FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

10.3 Treatments (study treatment, concomitant therapies, compliance)

The patients will be grouped into five mutually exclusive treatment groups based on the anti-diabetic treatment received:

1. Incretin based therapy group
2. Insulin group
3. Baseline insulin group - includes patients who receive insulin at baseline and thus not randomized.
4. Oral anti-diabetic (OAD) treatment group - patients who developed hyperglycemia that can be controlled by metformin or their background anti-diabetic treatment and thus are not randomized
5. No anti-diabetic treatment (NAD) group - includes patients who do not receive any anti-diabetic treatment during the core phase of the study.

The NAD group, baseline insulin group, and OAD group are the three observational arms that will be treated for 16 weeks during the core phase. The core treatment period of the two randomized arms, i.e., incretin based therapy group and insulin group, is varied and can be up to 32 weeks depending on when patients get randomized.

Treatment exposure will be summarized descriptively using SAS by disease and treatment groups.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized using SAS.

10.4 Primary objective

The primary objective is to evaluate the effect of initial treatment with incretin based therapy vs. insulin on glycemic control in patients with Cushing's disease or acromegaly who develop or worsen hyperglycemia on pasireotide, and cannot be controlled by metformin alone or

[redacted]

other background anti-diabetic treatments. The primary endpoint will be assessed at the Core EOP.

10.4.1 Variable

The primary variable is defined as the change from randomization in HbA1c (unit in %) at the time of assessing primary endpoint in incretin based therapy arm and insulin arm. For patients who require rescue treatment, the last HbA1c assessment before rescue treatment will be used for primary efficacy analysis.

10.4.2 Statistical hypothesis, model, and method of analysis

There is no formal hypothesis testing planned in this study. An estimate of the mean difference of the change from randomization in HbA1c between the two randomized arms will be reported along with 95% confidence interval (CI). Patients will be stratified by their disease and baseline glycemic status. Variance estimation will be based on the following analysis of variance (ANOVA) model using the two stratification factors as well as treatment as fixed effects. RAS will be used for primary analysis:

Change from baseline in HbA1c = Baseline glycemic status + Disease + Treatment + Error

Disease:

a. Cushing's disease
b. Acromegaly

Glycemic status at baseline:

a. HbA1c < 7 %
b. HbA1c ≥ 7%

Treatment:

a. Incretin based therapy group
b. Insulin group

10.4.3 Handling of missing values/censoring/discontinuations

For patients who discontinued the study or require rescue treatment before the time of assessing primary endpoint, the last HbA1c assessment collected 8 weeks after randomization will be carried forward for primary efficacy analysis. If the patient discontinued the study or used rescue treatment within 8 weeks after randomization, it will be considered missing for primary analysis.

10.4.4 Supportive analyses

Mean difference of change from randomization to the time of assessing the primary endpoint between two randomized arms, as well as the corresponding 95% confidence interval will be analyzed by ANOVA with disease state and baseline glycemic status as fixed effects. Patients taking rescue treatment before the time of assessing the primary endpoint will follow ITT rule, i.e., HbA1c assessment on Core EOP in each randomized arm will be utilized for analysis regardless of rescue treatment use. RAS will be used for supportive analysis. Subgroup analysis by disease and baseline HbA1c level may be performed.

[redacted]

In addition, the primary efficacy variable will be analyzed by analysis of covariance (ANCOVA) model with treatment and disease as classification variables and baseline HbA1c as the covariate. The least squares mean ("adjusted mean") of change from randomization for each treatment group and its standard error (SE), the difference between two treatment groups and the associated two-sided 95% CI for the difference will be obtained from the following ANCOVA model.

Change from baseline in HbA1c = intercept + Baseline HbA1c + Disease + Treatment + Error

Disease:

a. Cushing's disease
b. Acromegaly

Treatment:

a. Incretin based therapy group
b. Insulin group

10.5 Secondary objectives

The secondary objectives are to assess the overall effect of anti-diabetic intervention on the glycemic control, as well as the sustainability of glycemic control in the insulin arm and the incretin based therapy arm in patients with Cushing's disease or acromegaly. Safety and tolerability of pasireotide and anti-diabetic treatments will also be evaluated.

10.5.1 Key secondary objective(s)

Not applicable.

10.5.2 Other secondary efficacy objectives

10.5.2.1 Change in HbA1c and FPG to EOP

The change in HbA1c and FPG from baseline to the core EOP in patients who received pasireotide (FAS) will be summarized by treatment group using descriptive statistics. 95% confidence intervals will be provided for the changes from baseline.

10.5.2.2 Proportion of patients with an increase in HbA1c less than or equal 0.3%

The proportion of patients with an increase from baseline in HbA1c $\leq$ 0.3% at Core EOP will be summarized for each randomized arm. The corresponding 95% confidence interval will be estimated by exact method.

10.5.2.3 Change in HbA1c and FPG overtime

The change in HbA1c and FPG from randomization overtime and to the core EOP (only for FPG) will be summarized for each randomized arm. Descriptive statistics as well as 95% confidence intervals will be provided for the changes from baseline. Graphical presentation will also be used for change from randomization overtime in HbA1c and FPG.

[redacted]

10.5.2.4 Proportion received anti-diabetic rescue therapy

The proportion of patients who received anti-diabetic rescue therapy in incretin based therapy will be summarized. The corresponding 95% confidence interval will be estimated by exact method.

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

SAS will be used for safety analysis including both pre-randomized period and randomized treatment period. Randomized patients within SAS will be used to summarize main safety output during the randomized treatment period. All listings and tables will be presented by disease state when using SAS unless otherwise specified, safety outputs on randomized patients will be presented by disease state and by randomized arms. The overall observation period will be divided into three mutually exclusive segments:

1. Pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
2. On-treatment period: from day of first dose of study medication to 28 days after last dose of pasireotide s.c., and 84 days after last dose of pasireotide LAR, or the follow-up visit, whichever comes later. On-treatment period can be further divided into pre-randomized period and randomized treatment period as depicted in the visit evaluation schedule in Table 7-1.
3. Post-treatment period: starting at 28+1 days after last dose of pasireotide s.c., and 84 days + 1 day after last dose of pasireotide LAR, or the follow-up visit + 1 days whichever comes later.

10.5.3.2 Adverse events (AEs)

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

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 grades), type of AE, and relation to study treatment.

Deaths reportable as SAEs and non-fatal SAEs will be listed by patient and tabulated by type of adverse event.

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

For each specified SEC, number and percentage of patients with at least one event part of the SEC will be reported. In this study, SEC refers to AE of special interest.

[redacted]

10.5.3.3 Laboratory abnormalities

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

For laboratory tests where grades are not defined by CTCAE, results will be graded as low/normal/high based on laboratory normal ranges (NRs).

The following by-treatment summaries will be generated separately for hematology, clinical chemistry and urinary laboratory tests:

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

In addition to the above mentioned tables and listings, other exploratory analyses, might be specified in the RAP (Report and Analysis Plan).

10.5.3.4 Other safety data

ECG

- Data from ECG will be listed, notable values will be flagged, and any information collected will be listed as appropriate.
- Summary statistics will be provided at baseline and scheduled post-baseline time points for ECG variables PR, QRS, QT/QTcF interval and ventricular rate. Shift table from baseline to worst on-treatment result and summary statistics of changes from baseline will also be provided.
- Number and percentage of patients with clinically notable QT/QTcF interval values will be summarized.

Vital signs

Definitions of notably abnormal results have to part of the Clinical Development Plan (CDP), Master Analysis Plan (MAP), Clinical Study Protocol (CSP) and Report and Analysis Plan (RAP).

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

[redacted]

Hypoglycemia events

The number of treatment emergent hypoglycemia events, as well as the number of patients with hypoglycemia events will be summarized using SAS by treatment group. Hypoglycemia events will be defined based on CTCAE grade.

Thyroid function tests

Change from baseline to different time points for thyroid function tests will be summarized along with corresponding descriptive statistics.

Gallbladder examinations

Shift table of baseline to worst on-treatment result for gallbladder examinations will be provided.

10.5.3.5 Supportive analyses for secondary objectives

Not applicable.

10.5.4 Biomarkers

Not applicable.

10.5.5 Patient-reported outcomes

Not applicable.

10.6 Exploratory objectives

Not applicable.

10.7 Interim analysis

Not applicable.

10.8 Sample size calculation

There is no formal hypothesis testing planned in this study.

A total sample size of 68 randomized evaluable patients (in 1:1 allocation ratio to incretin based therapy and insulin) with at least 8 weeks of randomized treatment without any rescue anti-diabetic medication is required. In order to reach 68 randomized evaluable patients, approximately 79 patients will be randomized based on current drop-out/rescue rate prior to Week 8 (i.e., patients without 8 weeks of randomized treatment or took rescue medication prior to Week 8). The total number of enrolled patients will be based on the actual randomization (which occurs within 16 weeks after patients are enrolled) rate which will be monitored regularly.

The sample size was calculated to ensure that the half-width of the 95% confidence interval around the mean difference of the change from randomization to Week 16 (the subsequent scheduled visit after 16 weeks in randomization) in HbA1c (%) will be approximately 0.5%.

[redacted]

The calculation was performed using R version 3.00 and based on a standard deviation of 1.03%, which was consistent with the results from the CSOM230B2305 phase III trial.

10.9 Power for analysis of key secondary variables

Not applicable.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

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

11.2 Responsibilities of the investigator and IRB/IEC/REB

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

11.3 Informed consent procedures

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

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

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

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

11.4 Discontinuation of the study

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

11.5 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

11.5.1 Communication and Publication of Clinical Trial Results

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

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

Accordingly, ALL AUTHORS MUST HAVE:

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

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

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s)

[redacted]

and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

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

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

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

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

11.7 Confidentiality of study documents and patient records

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

11.8 Audits and inspections

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

11.9 Financial disclosures

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

[redacted]

12 Protocol adherence

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

12.1 Amendments to the protocol

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

13 References (available upon request)

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[redacted]

14 Appendices

14.1 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 should be discussed with the Novartis Medical Monitor.

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

[redacted]

14.2 Appendix 2: Formula to calculate QTcF

If the ECG machine at your site does not automatically provide QTcF then use the following formula to calculate it.

$QTcF = QT_{Interval} / (RR_{Interval})^{1/3}$ in msec.

Use the $QT_{Interval}$ and $RR_{Interval}$ provided by the ECG machine.

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

[redacted]

14.3 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.

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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 glucose reacts to exercise. Bring a snack if you'll be active for a few hours.

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