Recordati Clinical Development & Medical Affairs

SOM230 (pasireotide)

CSOM230B2410

Non-interventional study for the generation of long term safety and efficacy data of pasireotide s.c. in patients with Cushing's disease (Post-Authorization Safety Study)

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Document type:	Amended Protocol Version
EU PAS register number	EUPAS3199
Version number	03 (Clean)
Development phase	Non-interventional study
Document status	Final
Release date	06-May-2020
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CRO	IQVIA

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List of abbreviations

ACTH	Adrenocorticotropic Hormone
AE	Adverse Event
AESI	Adverse event of special interest
ALT	alanine aminotransferase
APTT	Partial Thromboplastin Time
AST	aspartate aminotransferase
ATC	Anatomical Therapeutical Chemical
b.i.d.	bis in diem/twice a day
BIPSS	Bilateral Inferior Petrosal Sinus Sampling
CD	Cushing's Disease
CI	Confidence Interval
CRF	Case Report/Record Form
CRH	Corticotrophin-Releasing Hormone
CRO	Contract Research Organization
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
EDC	Electronic Data Capture
ESE	European Society of Endocrinology
FDA	Food and Drug Administration
FPG	Fasting Plasma Glucose
GH	Growth Hormone
GIP	Glucose-Dependent Insulinotropic Polypeptide
GLP	Glucagon-Like Peptide 1
HbA1C	Hemoglobin A1C
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IGF-1	Insulin-like Growth Factor
IRB	Institutional Review Board
LDDST	Low-Dose Dexamethasone Suppression Test
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRI	Magnetic Resonance Imaging
NYHA	New York Heart Association
PT	Prothrombin Time
QoL	Quality of Life
RAP	Report Analysis Plan
RBC	Red Blood Cells
REB	Research Ethics Board
RMP	Risk Management Plan
s.c.	sub-cutaneous
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SI units	International system of units
SSA	Somatostatin Analogue
TSH	Thyroid Stimulating Hormone
UFC	Urinary Free Cortisol

ULN	Upper Limit Normal
WBC	White Blood Cells
WHO	World Health Organization
γGT	Gamma Glutamyl Transpeptidase

Amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
1	20-Sep-2013	Sections 1, 2, 3, 6, 7 and 8	Amendment	Discussion with Health Authorities on data collection in large Cushing disease patient population treated with pasireotide s.c.
2		Sections 3, 6 and 7	Amendment	Modifications for publication of study results Update to lists and descriptions of adverse events Description of frequency of data transfers
3	06-May-2020	All document	Amendment	Change of Sponsorship from Novartis to Recordati Inclusion of IQVIA as CRO managing a number of study activities on behalf of Recordati

Amendment 3 (06 May-2020)

Amendment rationale

Novartis has signed an agreement to transfer the worldwide rights of Signifor® and Signifor® LAR to Recordati. Within the framework of such agreement, the two Companies agreed a sponsorship transfer of this study with pasireotide from Novartis to Recordati.

The purpose of this substantial amendment is to reflect the change in sponsorship, and to add IQVIA as the CRO in charge for performing some study-related activities on behalf of Recordati.

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 underline for insertions.

- All sections: were updated to substitute the name of the current sponsor Novartis with the name of the new sponsor Recordati or of IQVIA on behalf of Recordati, as applicable.

IRBs/IECs

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

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

Amendment 2 (25-Jul-2016)

Amendment rationale

The purpose of this protocol amendment is to update the section on publication of study results. In addition, the description and list of adverse events of special interest (AESI) has been updated, and a list of special scenarios to the definition of adverse events (AE) has been added, in alignment with current program standards. Furthermore, the transfer of non-serious adverse events data to Novartis DS&E has been specified, i.e. to occur on a periodic basis but not less frequently than once a month. Few typographical errors were corrected and an incomplete sentence removed.

Patient enrollment in the study started in March 2013 and is planned to close in March 2021; the last patient's follow-up visit in the study is planned to be in April 2024. Due to the long duration of the study, publication of study results will not only occur upon study completion but be allowed at different timepoints throughout the study such as the yearly interim analyses. Furthermore, regional and/or local analyses and publications will also be allowed once analysis and publication of the overall population is performed.

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 underline for insertions.

List of abbreviations: updated with new abbreviations

Summary of previous amendments Amendment 1: addition of a sub-header

Section 3.5.2.1: The transfer of information on non-serious AEs to Novartis DS&E has been specified to occur on a periodic basis but not less frequently than once a month.

Section 3.5.2.1: Inclusion of a list of special scenarios that are also considered to be adverse events

Section 3.5.2.3: Updated description and list of AESIs

Section 3.5.2.4: Removal of incomplete sentence

Section 6.6: Updated to allow for additional interim analyses for regulatory or publication purpose

Section 7.2.5: Updated to allow for regional and/or local analyses and publications.

IRBs/IECs

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

Summary of previous amendment(s)

Amendment 1

Amendment rationale

This amendment has been implemented based on discussion with Health Authorities. It addresses the following key items of the original protocol released for the study:

Pasireotide s.c. is being made available in several countries. As it is the first approved medication targeting the underlying cause of Cushing's disease, there is a growing interest to follow-up patients treated with the compound. Therefore, one of the main reasons to issue the amendment is to collect data in a large patient population affected by Cushing's disease. As a consequence this study will enroll up to 200 patients but not less than 100 patients.

Furthermore, more disease specific background information on potential risk factors for hyperglycemia, liver-related adverse events, QT prolongation, atypical infections and adrenal insufficiency will be collected. This information is related to some adverse drug reactions recorded during the treatment with pasireotide.

Even though this is an observational trial, the experience with the medication is still limited to clinical trials. Therefore, it is considered very useful to provide a list of suggested schedules of assessments that can help the investigator following up the patients treated with pasireotide. This would lead to a more consistent approach to the use of the medication.

Since the enrollment target should primarily be based on new users (pasireotide naïve patients starting treatment with pasireotide s.c. on the day of inclusion into the study), and based on the fact that pasireotide s.c. is already available in many countries by the time of study implementation it is considered challenging to enroll pasireotide naïve patients, the enrollment period was extended to 96 months.

In order to ensure patients' safety and completeness of study data a follow-up period of 3 months will be implemented for patients lost to follow-up. The investigator is requested to show "due diligence", for the first 3 months after the last known date the patient took pasireotide, by documenting in the source documents steps taken to contact the patient, e.g. evidence of two certified letters, dates of telephone calls, sent emails.

Specific Health Authorities require reporting of non-serious adverse events on a monthly basis. Therefore, the protocol requires investigators to update the electronic case report form at least once a month so that the database reflects most up-to-date safety information once per month.

SAEs should be collected even if they may be related to the underlying condition. Analyses and careful interpretation of data should allow for the possibility of relationship of the SAE to the underlying condition. Therefore, the following event will be removed from the events not considered to be serious adverse events for hospitalizations: "hospitalization for any SAEs that are expected due to the condition being treated, including if the SAE is a primary outcome measure, and whether there has been a clear agreement with regulators not to consider these as SAEs, provided the information is collected elsewhere"

In order to ensure consistent reporting of adverse events the protocol requires adverse event reporting according to CTCAE version 3.0.

Data will be summarized and displayed by time intervals based visit windows rather than by a strict visit schedule.

A Full Analysis Set (FAS) has been defined.

Incidence rates by person-time of exposure and person-time of observation will be reported.

Missing data handling has been described in more detail.

Further clarification on sample size and power considerations have been provided.

Minor discrepancies have been corrected and additional minor information has been added on the statistical hypothesis, model and method of analysis.

As of the release date of this amendment, 5 patients have been enrolled in this study. There is an anticipated impact of this amendment on the duration of recruitment and on the release of results.

Changes to the protocol

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

The major changes to the protocol, and the sections affected, are detailed below.

List of abbreviations

- EMA (European Medicines Agency) removed from the list of abbreviations as long term safety follow-up study has been requested by additional Health Authorities and study is applicable to more than one geographic region.
- 1. Introduction
  - “EMA” has been replaced by Health Authorities.
- 2.2.1 Endpoints for secondary objectives
  - Clarification that change from last dose will be evaluated for all available “continuous” safety and efficacy parameters
- 3.1.1 Safety and tolerability assessments
  - Redundancy was removed from this section “for all available parameters”
  - Removal of request for regular monitoring and recording of safety data as this has now been described in the suggested table of assessments
  - Addition of recommendation to report data on history of smoking, history of alcohol use, and presence of hepatitis B and C infection in medical history
- 3.1.2 Efficacy assessments
  - Redundant text “for all available parameters” removed

- 3.3.1 Patient Population
  - Country and site number increased as this long term safety follow-up study has been requested by additional Health Authorities outside of Europe and new requirement of including patients starting pasireotide s.c. at time of enrollment has been added. Timelines and number of patients to be included has been updated as well.
- 3.4.1.1 Treatment discontinuation
  - Clarification that Patients who discontinue pasireotide s.c. treatment because of an adverse event, must be followed by the investigator until resolution of the AE or until 3 months following discontinuation of drug whichever is longer.
  - Addition of details on “lost to follow-up” procedure such as requirement of two certified letters, telephone call and emails.
- 3.4.1.2 Medical history and prior/concomitant treatment of Cushing’s disease
  - Addition of recommendation to report data on history of smoking, history of alcohol use, and presence of hepatitis B and C infection in medical history
- 3.5 Visit Schedule and Assessments
  - “Suggested schedule of assessments” has been included in protocol to help encourage more uniform data collection across study sites and patients. 3.5.2.1 Adverse events
- 3.5.1 Patient demographics and other baseline characteristics
  - Addition of recommendation to report data on history of smoking, history of alcohol use, and presence of hepatitis B and C infection in medical history
- 3.5.2.1 Adverse events
  - Addition of further details of adverse event reporting
  - Addition of requirement of reporting adverse events according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0
- 3.5.2.2 Serious Adverse events
  - Removal of event from the events not considered to be serious adverse events for hospitalizations: “hospitalization for any SAEs that are expected due to the condition being treated, including if the SAE is a primary outcome measure, and whether there has been a clear agreement with regulators not to consider these as SAEs, provided the information is collected elsewhere”
  - Addition of details on adverse events of special interest for pasireotide s.c.
- 3.5.3.1 Laboratory evaluations
  - In order to ensure availability of baseline for UFC efficacy parameter for patients who did not have an UFC assessment at their first visit requirement of entering the last available UFC value before study entry will be collected on the CRF.

- 6 Statistical methods
  - Clarification that data will be summarized and displayed by time intervals based visit windows rather than by a strict visit schedule
  - Clarification that for patients who discontinue treatment prior to the 3-year observation period, their safety and efficacy parameters will be reported according to the time window that corresponds to Day of last dose of pasireotide s.c 90 days.
  - Clarification that continuous variables will be summarized by number of patients, mean, standard deviation, minimum, median and maximum. Categorical variables will be summarized by absolute and relative frequencies. Counts of missing values for both continuous and categorical variables will be reported. Results with and without imputation will be reported.
- 6.1.1 Full Analysis Set (FAS)
  - Definition of Full Analysis Set added
- 6.2 Patient demographics/other baseline characteristics
  - Clarification that counts of missing values for both continuous and categorical variables will be reported
- 6.3 Treatments (pasireotide s.c, concomitant therapies)
  - Clarification that treatment includes prescribing information on the pasireotide s.c. start and stop dates, dose, dose changes and reason for changes
  - Clarification that incidence rates by person-time of exposure and incidence rates by person-time of observation with their corresponding 95% confidence interval will be reported.
- 6.4.2 Statistical hypothesis, model, and method of analysis
  - Clarification that the study is exploratory in nature and no formal hypothesis testing is planned
- 6.5.1 Efficacy evaluation
  - Clarification that the efficacy analysis will be performed on the FAS
  - Deletion of “Incidence of Adverse events…” efficacy endpoint as this constitutes a safety endpoint
- 6.5.1.2 Absolute and percentage change from baseline secondary efficacy endpoints
  - Deletion of LOCF method
- 6.5.1.3 Absolute change between the last assessment on drug and 3 months later for continuous secondary efficacy endpoints added
  - New header added
- 6.5.1.5 Handling of missing data
  - New paragraph added

- 6.5.2 Safety evaluation
  - Clarification that for all safety analyses the safety set will be used
  - Clarification that for continuous safety variables, the change from the last dose of pasireotide s.c. to 3 months after permanent discontinuation of pasireotide s.c. for patients that discontinue pasireotide s.c. prior to completing the 3-year observation period will be summarized.
  - Clarification that safety analysis will be stratified by incident or prevalent use of the drug.
- 6.5.2.2 Laboratory evaluations
  - Clarification that no imputations for missing values will be done for laboratory variables and they will be identified as missing
- 6.5.2.3 Other safety data
  - Clarification that no imputations for missing values will be done for laboratory variables and they will be identified as missing
- 6. 5.3 Subgroup Analysis
  - Clarification that subgroup analysis will be performed for other countries than Germany on request.
- 6.6 Interim Analyses
  - "EMA" replaced by Health Authorities.
  - Clarification that analysis of study will occur when all patients complete the study.
- 6.7 Sample size and power considerations
  - Enrollment information updated
- 7.1.3 Instructions for completing adverse event case report forms
  - Section deleted as information of this chapter has been added to section 3.5.2.1
- 8 References
  - Reference for Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0 has been added.

The term "trial" has been replaced by "study" across the entire protocol.

IRBs/IECs

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

The changes described in this amended protocol may require IRB/IEC approval prior to implementation according to local regulation. In addition, if the changes herein affect the Informed Consent, sites may be required according to local regulation to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

1 Introduction

Cushing's disease (CD) is a devastating endocrine disease that is caused by an adrenocorticotropic hormone (ACTH) secreting pituitary adenoma. Epidemiological studies indicated an annual incidence of 0.7-2.4 per million population (Lindholm et al 2001). However, a recent study performed in Belgium reported a much higher prevalence of CD (Daly et al 2006): 55 per million population. Eighty percent of these tumors can be classified as microadenomas, and 20% as macroadenomas. The elevated ACTH levels secreted by these tumors stimulate the adrenal glands to produce excess cortisol, leading to the subsequent development of the clinical signs and symptoms of hypercortisolism. Cushing's disease is rare, associated with severe morbidity and premature mortality and most commonly affects adults aged 20-50, primarily females. Patients suffer from this disease for many years before coming to medical attention and appropriate diagnosis.

The most common pathological finding in these patients is bilateral hyperplasia of the adrenal cortex due to excessive ACTH secretion. The primary clinical symptoms of Cushing's disease are due to hypercortisolism, and include the following:

- Change in body habitus: moon face, supraclavicular fat pad, buffalo hump
- Hirsutism on face, neck, chest, abdomen, thighs
- Skin changes with easy bruising, purplish striae, reddening of the cheeks due to weakened connective tissue
- Generalized weakness and fatigue
- Wasting of musculature, particularly proximal muscles
- Menstrual disorders in females
- Decreased fertility and/or libido
- Hypertension
- Weight gain
- Diabetes mellitus
- Depression, mood and behavior disorders
- Sleep disturbances
- Osteopenia/osteoporosis

Most patients also develop a high set-point for feedback inhibition of ACTH secretion by cortisol. In addition to the patient's medical history and physical examination, several laboratory tests and diagnostic techniques are available for the diagnosis of Cushing's disease. Twenty four hour urinary free cortisol (UFC) measurements, blood sampling for serum cortisol levels, and the low-dose dexamethasone suppression test (LDDST) are widely used as screening tests for the diagnosis of Cushing's disease (Newell-Price et al 1998). To distinguish Cushing's disease from other forms of hypercortisolism, a confirmation of a pituitary source of ACTH secretion is needed. This includes an inappropriately normal or elevated plasma ACTH level and evidence of pituitary tumor on magnetic resonance imaging (MRI) scan or confirmed by bilateral inferior petrosal sinus sampling (BIPSS) after corticotrophin-releasing hormone (CRH) stimulation test (evidence of a pituitary source of ACTH). It is generally accepted that if the ratio of adrenocorticotrophin concentration in the inferior petrosal sinuses to peripheral

blood is greater than or equal to 3.0 after CRH stimulation, a diagnosis of Cushing's disease can be made (Oldfield et al 1991).

Pituitary resection of the adenoma is the current first-line therapy for Cushing's disease, but surgical failure rates are as high as 25-30% even in the hands of the most experienced neurosurgeons. Additionally postoperative recurrence rates are as high as 20% by 5 years (Bochicchio 1995, Sonino 1996). Surgery is in many cases complicated by hypopituitarism, which requires complicated life-long hormonal replacement therapy necessary to sustain life. Treatment usually focuses on replacing the target hormones rather than the pituitary hormones, and in patients who have multiple axis deficiencies maintenance with multiple replacement hormones can be difficult, and requiring close and constant medical monitoring, and can be expensive (Swearingen et al 1999).

Irradiation of the pituitary is another option but it may take many years to be effective and it is curative in only 15 to 45% of the cases. In addition, due to its lack of specificity the procedure also often results in hypopituitarism. Furthermore, there is a 1 to 2% risk of development of secondary tumors in the field of radiation over subsequent years (Orth 1995).

When surgery and/or irradiation fail, or for those patients for whom such therapies are not an option, the remaining alternative is pharmacological treatment. No drug is currently approved for the treatment of Cushing's disease and the ones which physicians are using are fraught with suboptimal results and significant side effects (Miller 1993, Nieman 2002) preventing their long term use required in the management of CD. Therefore, a safe and effective targeted medical therapy is highly desirable in this patient population.

Pasireotide (SOM230) is a novel cyclohexapeptide, somatostatin analogue. Pasireotide exhibits a unique binding profile with high affinity to four of the five known human somatostatin receptor subtypes (sst1, 2, 3 and 5).

A phase III [CSOM230B2305] study evaluated the efficacy and safety of two doses of pasireotide s.c. (600 and 900 µg s.c. b.i.d., respectively) in 162 patients with moderate to severe Cushing's disease by evaluating the normalization of UFC values at 6 months of treatment. The study showed that pasireotide is an active medication in the treatment of hypercortisolism in CD. At month 6, 26.3% of patients who were randomized to pasireotide 900 µg b.i.d. were considered to be responders (patients with a mean UFC $\leq$ ULN, who did not up-titrate the dose during the 6-month treatment period). In the 600 µg b.i.d. dose group, 14.6% of patients were responders. The mean UFC decreased in both treatment groups. The mean absolute change from baseline in mean UFC were -463.4 and -363.9 nmol/24h respectively for the 600 µg and 900 µg b.i.d. groups (which represent a median decrease from baseline of approximately 47% in both study groups). Overall, as mean UFC decreased continuous measures of the signs of Cushing's disease (blood pressure, weight and serum lipid levels) improved. Overall pasireotide was well tolerated. The majority of the AEs reported are consistent with the known adverse drug reactions of SSAs. The most commonly affected system organ classes were gastrointestinal disorders, general disorders, and metabolism and nutrition disorders. The most frequent AEs were diarrhea, nausea and hyperglycemia. As expected in successful therapies for hypercortisolism, adverse events related to cortisol withdrawal (hypocortisolism) were reported in some patients, for which a dose decrease resulted in effective management of the AE.

However, study durations are limited and long-term efficacy and safety is also limited. The pasireotide-induced effects of long-term hyperglycemia and other potential long-term effects (i.e. on GH/IGF-1 axis) could not be addressed by the pivotal trial [CSOM230B2305]. As Health Authorities require such data, the purpose of this non-interventional study is therefore to generate long term safety and efficacy data during the long-term treatment of pasireotide s.c. in patients with Cushing's disease in a real life setting.

2 Study objectives

2.1 Primary objective

To document the long-term safety and tolerability profile of pasireotide s.c. when administered as monotherapy or in combination with other therapies in patients with Cushing's disease.

2.1.1 Endpoint for primary objective

Incidence of pasireotide s.c.-related adverse events and serious adverse events during the 3-year observation period

2.2 Secondary objectives

- To document the short and long-term efficacy of pasireotide s.c. as measured by the proportion of patients that reach mean UFC ≤ ULN at 1, 3, 6, 12, 24 and 36 months after enrolling into the study
- To document the changes of biochemical measures of disease activity (mean UFC, serum cortisol, serum cortisol after dexamethasone testing, salivary cortisol, ACTH and fasting serum lipid profile) over time
- To document normalization of biochemical measures of disease activity (serum cortisol, serum cortisol after dexamethasone testing, salivary cortisol and ACTH) over time, where normalization refers to being within the upper and lower limit of normal ranges
- To document the changes of measures of clinical signs and symptoms (blood pressure, body weight, body mass index, waist circumference) over time
- To document the changes in clinical symptoms of Cushing's disease over time
- To document the changes in safety and efficacy parameters over a period of 3 months after discontinuing pasireotide s.c. treatment for patients that permanently discontinue pasireotide s.c. prior to completing 3-year observation period
- To document the changes in tumor size over time
- To document the changes in patient-reported outcome questionnaires (Cushing QoL and EURO QoL)
- To document the overall safety and tolerability of pasireotide s.c.

2.2.1 Endpoints for secondary objectives

- Proportion of patients with a mean UFC ≤ ULN at 1, 3, 6, 12, 24 and 36 months after enrolling into the study
- The absolute and percentage change from baseline in biochemical measures of disease activity (mean UFC, serum cortisol, serum cortisol after dexamethasone testing, salivary cortisol, ACTH and fasting serum lipid profile) over time
- Proportion of patients achieving normalization of biochemical measures of disease activity (serum cortisol, serum cortisol after dexamethasone testing, salivary cortisol and ACTH) over time
- The absolute and percentage change from baseline in clinical signs and symptoms (blood pressure, body weight, body mass index, waist circumference) over time
- The proportion of patients with favorable shift from baseline in clinical symptoms of Cushing's disease over time
- The change from the last dose of pasireotide s.c. to 3 months after permanent discontinuation of pasireotide s.c. for patients that discontinue pasireotide s.c. prior to completing the 3-year observation period. This change will be evaluated for all available continuous safety and efficacy parameters
- The absolute and percentage change from baseline in tumor size over time
- The absolute and percentage change from baseline in patient -reported outcome questionnaires (Cushing QoL and EURO QoL) over time
- Incidence of Adverse events and assessments of vital signs, blood pressure, heart rate, body temperature, blood glucose (fasting plasma glucose, HemoglobinA1c), hormones (GH, IGF-I, TSH/free T_4), liver enzymes (AST, ALT, alkaline phosphatase, γGT, total bilirubin), hematology, electrolytes, immunological events (e.g., allergic reactions: rash, pruritus, injection site reactions), gallbladder ultrasound and ECGs assessment values

3 Investigational plan

3.1 Overall study design

This is a non-interventional, multinational, multi-center post-marketing study, to further document the safety and efficacy of pasireotide s.c. administered in routine clinical practice in patients with Cushing's disease.

Patients with Cushing's disease and treated with pasireotide s.c. alone and in combination with other therapies will be monitored. For this study, each enrolled patient will be followed up for 3 years after enrollment. Patients who permanently discontinue pasireotide s.c. prior to completing the 3-year observation period will be followed up for 3 months after the last dose of pasireotide s.c.

3.1.1 Safety and tolerability assessments

All safety assessments will be collected from patient's enrollment into the study by signing the informed consent or acknowledging an equivalent document (e.g., written information) as per country regulation until the last dose of pasireotide s.c. at the patient's last follow-up visit within the 3 year observation period or until 3 months after the last dose for patients who permanently discontinue pasireotide s.c. prior to completing 3-year observation period.

- Adverse events and Serious Adverse Events will be followed-up and collected from patient's enrollment into the study until 28 days after the last dose of pasireotide s.c. at the patient's last follow-up visit. Adverse events and Serious Adverse Events will be collected until 3 months after the last dose for patients who permanently discontinue pasireotide s.c. prior to completing 3-year observation period.
- Special safety assessments will be collected from patient's enrollment into the study until the last follow-up visit as available or until 3 months after the last dose for all available safety parameters, for patients who permanently discontinue pasireotide s.c. prior to completing the 3-year observation period. Safety data to be collected include: vital signs, blood pressure, heart rate, body temperature, blood glucose (fasting plasma glucose, HemoglobinA1c), hormones (IGF-1, GH, TSH/free T_4), liver enzymes (AST, ALT, alkaline phosphatase, γGT, total bilirubin), hematology, electrolytes, immunological events (e.g., allergic reactions: rash, pruritus, injection site reactions), gallbladder ultrasound and ECGs.
- Medical history including history of smoking, history of alcohol use, presence of hepatitis B and C infection will be recorded at patient's entry in the study. Prior/concomitant medications/significant non-drug therapies (e.g., surgery, radiation) will be collected from patient's enrollment into this study until the last follow-up visit as available or until 3 months after the last dose for for patients who permanently discontinue pasireotide s.c. prior to completing the 3-year observation period.

3.1.2 Efficacy assessments

All efficacy assessments will be collected from patient's enrollment into this study until the last follow-up visit for patients who complete the 3-year observation period or until 3 months after the last dose for patients who permanently discontinue pasireotide s.c. prior to completing the 3-year observation period.

- Urinary Free Cortisol (UFC). In general UFC is determined by collecting two or three 24-hour urine samples and calculating the mean. However routine site procedures may also only foresee one single urine sample to assess UFC. The frequency of UFC determination will probably vary from the initiation of treatment (when UFC values will be performed more frequently than at monthly interval) as compared to the time after obtaining control.
- Biochemical measures of disease activity: serum cortisol, serum cortisol after dexamethasone testing, salivary cortisol, plasma ACTH and fasting serum lipid profile.
- Measures of clinical signs and symptoms: Blood pressure, body weight, body mass index, waist circumference, clinical symptoms of Cushing's disease.
- Changes in tumor size as measured by MRI or other imaging techniques
- Changes in the quality of life score determined from a patient reported quality of life questionnaire (Cushing QoL and EURO QoL).

3.2 Discussion of design

This is a non-interventional, multinational, multi-center post-marketing study, to further document the safety/tolerability and efficacy of pasireotide s.c. in patients with Cushing's disease.

This study is observational in nature and does not impose a therapy protocol, diagnostic/therapeutic interventions or a visit schedule. Patients with Cushing's disease who are treated with pasireotide s.c. will be followed up for 3 years from patient's enrollment into this study, unless the patient discontinues pasireotide s.c. prematurely. If patients discontinue pasireotide s.c. prior to completing the 3 year observation period then any available safety and efficacy parameter will be collected until 3 months after the last dose of pasireotide s.c.

The timeframe of 3 years will allow to investigate the long-term safety/tolerability and efficacy of pasireotide s.c. including important safety evaluation on pasireotide s.c.-induced glycaemia effects, as well as the long-term changes of pituitary hormones and their by-products. The 3 year observation period is long enough to allow for the stabilization of the biochemical measures of disease activity (i.e. UFC and plasma ACTH), thus reducing the confounding effect of acute changes in UFC on the long-term safety measures (such as glycaemia, and pituitary hormones).

3.3 Study population

3.3.1 Patient population

The patient population will consist of male and female patients aged 18 years or older with a diagnosis of Cushing's disease for whom surgery has failed or for whom surgery is not an option and who are treated with pasireotide s.c. Investigators need to ensure that patients enrolled in this study meet the inclusion and exclusion criteria described in Section 3.3.1.1.

Approximately 100 sites in about 35 countries will participate in this study.

The study will enroll a minimum of 100 patients to a maximum of 200 patients. Recruitment is expected to take approximately 96 months. The actual sample size may differ from this planned number.

Inclusion and exclusion criteria

3.3.1.1 Inclusion criteria

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

- Written informed consent or equivalent document (e.g., written information) as per country regulation prior to registration of any patient data
- Male or female patients aged 18 years or older with a diagnosis of Cushing's disease for whom surgery has failed or for whom surgery is not an option
- Patients must be treated with pasireotide s.c. started either at the first visit for this study or prior to study entry

3.3.1.2 Exclusion criteria

- Patients with ectopic ACTH-dependent Cushing's syndrome

- Patients with adrenal Cushing's syndrome
- Patients with Pseudo Cushing's syndrome

3.4 Treatments

3.4.1 Pasireotide therapy

This observational study will include patients who are prescribed commercial pasireotide s.c. medication. The overall treatment pattern with pasireotide s.c. should be consistent with the local prescribing information.

3.4.1.1 Treatment discontinuation

Patients who permanently discontinue treatment with pasireotide s.c. prior to the 3-year observation period will have to be withdrawn from this study. Patients who discontinue pasireotide s.c. treatment because of an adverse event, must be followed by the investigator until resolution of the AE or until 3 months following discontinuation of drug whichever is longer.

All available safety and efficacy parameters will be collected for a period of 3 months following the last dose of pasireotide s.c. for patients who permanently discontinue pasireotide s.c. prior to completing the 3-year observation period.

Patients may voluntarily withdraw from this study or discontinued at the discretion of the investigator at any time. If such withdrawal occurs the investigator should determine the primary reason for a patient's premature withdrawal from this study. The withdrawal reason should be categorized into one of the following:

- Adverse event(s)
- Protocol deviation
- Subject withdrew consent or equivalent document (e.g., written information) as per country regulation
- Lost to follow-up
- Administrative problems
- Death
- Unsatisfactory therapeutic effect

For patients who are lost to follow-up, the investigator should show "due diligence", for the first 3 months after the last known date the patient took pasireotide, by documenting in the source documents steps taken to contact the patient, e.g. evidence of two certified letters, dates of telephone calls, sent emails.

3.4.1.2 Medical history and prior/concomitant treatment of Cushing's disease

Medical history of Cushing's disease including history of smoking, history of alcohol use, and presence of hepatitis B and C infections will be collected at patient's entry to the study. Prior/concomitant treatments and significant non-drug therapies for the management of Cushing's disease will also be collected as available when patients enroll into the study.

3.5 Visit schedule and assessments

This study is observational in nature and does not impose a therapy protocol, diagnostic/therapeutic interventions or a visit schedule. However, in order to help encourage more uniform data collection across study sites and patients a suggested schedule of assessments has been provided in Table 3-1.

Patients will be treated with pasireotide s.c. according to the investigator's judgment and in accordance with the local (country-specific) pasireotide s.c. prescribing information. Available data will be collected at patients‘ visits to their site.

Table 3-1 Suggested schedule of assessments

Visit/Frequency	Baseline	Monthly	Every 3 months	Every 6 months	Every 12 months	End of Treatment	End Of study
Informed Consent	x						
Demography	x						
Inclusion/Exclusion Criteria	x						
Relevant medical history/Current medical conditions (history of smoking, history of alcohol use, presence of hepatitis B and C infections)	x						
Cushing's disease history	x						
Prior medications - For Cushing's Disease	x						
Coagulation test (Prothrombin time, APTT)	x					x	x
Vital Signs	x	x	x	x	x	x	x
Pregnancy test	x	x	x	x	x	x	x
Clinical symptoms of Cushing's disease	x		x			x	x
Glycemic status, FPG	x [1]	x [2]				x [3]	x [3]
Glycemic status, HbA1c	x [1]		x			x [4]	x [4]
Salivary cortisol	x	x [5]	x			x	x
Serum cortisol after dexamethasone	x	x [5]	x			x	x
24 hour urine collection - Urinary free cortisol	x	x[5]	x			x	x
Pituitary imaging local analysis (MRI/CT scan)	x				x	x	x
LFTs (ALT, AST, Alkaline phosphatase)	x [1]	x [6]	x			x	x
12 lead ECG evaluation - local analysis	x[1,7]		x			x	x
Hematology/Blood Chemistry *	x			x		x	x
Thyroid function tests (TSH, Free T4)	x				x	x	x
Gallbladder imaging	x [1]			x	x	x	x
Cushing's syndrome QoL/ Euro QoL-5D health QoL/ Patient Reported outcome (PRO)	x			x		x	x

Visit/Frequency	Baseline	Monthly	Every 3 months	Every 6 months	Every 12 months	End of Treatment	End Of study
Dose Administration Record-Pasireotide s.c	x	At each visit				x	x
Adverse Events	x	At each visit				x	x
Concomitant Medication	x	At each visit				x	x

[1] prior starting treatment with pasireotide s.c
[2] self-monitoring of blood glucose and/or FPG every week for the 1st two to three months and periodically thereafter, as clinically appropriate.
[3] Monitoring of FPG 4 weeks after the end of treatment
[4] Monitoring of HbA1c 3 months after the end of treatment
[5] every month for the first 3 month and then every 3 months
[6] Monitoring of liver function after one, two, four, eight and twelve weeks
[7] one week after start of treatment, QTcF/QTcB prolongations> 480 msec have to reported as adverse events
* **Hematology**: WBC, RBC, Hemoglobin, Hematocrit, Platelets, Neutrophils, Lymphocytes, Eosinophils, Basophils, Monocytes
Blood chemistry: γGT, α-amylase, Total bilirubin, Indirect bilirubin, Direct bilirubin, Sodium, Potassium, Magnesium, GH, IGF-1, PT, Plasma ACTH, Triglyceride, Cholesterol,, LDL, HDL

Recommended assessments are specified and listed in the local product label.

3.5.1 Patient demographics and other baseline characteristics

Standard demographic information (demography, vital signs) and medical history (including history of smoking, history of alcohol use, hepatitis B and C infection)/current medical conditions, concomitant medications and significant non-drug therapies will be collected as available.

3.5.2 Safety assessments

Safety assessments to be collected in this study will consist of all adverse events, including serious adverse events. Adverse events and Serious Adverse Events will be reported and collected from patient's enrollment into the study until 28 days after the last dose of pasireotide s.c. at the patient's last follow-up visit. Adverse events and Serious Adverse Events will be collected until 3 months after the last dose for patients who permanently discontinue pasireotide s.c. prior to completing 3 years of treatment.

3.5.2.1 Adverse events

Information about all adverse events including serious adverse events (SAEs), whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, must be collected and recorded in the Adverse Event section of the study database (eCRF) irrespective of causal association. The investigator has to include information on all AEs in the individual patient eCRFs. The investigator has to commit to updating this information on a periodic basis but not later than once a month. Information on non-serious AEs is then transferred from the study database to Recordati by PPD data management on a periodic basis but not less frequently than once a month.

All AEs including SAEs occurring in association with exposure to another Recordati drug, if applicable, also have to be notified for recording in the Recordati safety database. Adverse reactions identified for non-Recordati products should be reported to the local Health Authority in accordance with national regulatory requirements for individual case safety reporting or the Marketing Authorization Holder; these will not be recorded in the Recordati safety database.

An adverse event is any undesirable sign, symptom or medical condition occurring on treatment with pasireotide s.c. even if the event is not considered to be related to pasireotide s.c. Medical conditions/diseases present before starting pasireotide s.c. treatment are only considered adverse events if they worsen after starting pasireotide s.c. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant or require therapy, and are recorded in the Adverse Events section. Adverse events will be collected after patients have signed the informed consent or acknowledged an equivalent document (e.g., written information) as per country regulation.

Adverse events will be assessed according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0. If CTCAE grading does not exist for an adverse event (document available upon request), the severity of mild, moderate, severe, and life-threatening, **or** grades 1 - 4, will be used.

In addition, all reports of the following special scenarios are also considered an adverse event irrespective if a clinical event has occurred:

- Drug-drug or drug-food interaction
- Drug use during lactation
- Lack of efficacy
  Reports of lack of efficacy without an associated clinical event must be recorded on the AE CRF even if lack of efficacy parameters are being collected and recorded elsewhere within the study database.
- Overdose
- Intentional drug abuse and misuse
- Medication errors including drug maladministration
- Dispensing or prescribing errors

Reports of overdose, drug abuse and misuse, drug maladministration and dispensing errors/medication errors without an associated clinical event must be recorded on the AE CRF irrespective of whether or not the information is also being captured on the drug administration record form.

- Drug dependence or addiction
- Withdrawal reaction/syndrome or rebound symptoms
- Unexpected beneficial effect
- Treatment non-compliance (with clinical symptoms)

Note: Occupational or accidental exposure, for example of study personnel or family members of the patient should be reported to the local Health Authority in accordance with national regulatory requirements for individual case safety reporting or Recordati as a spontaneous report.

Any treatment of any adverse event should be recorded on the Adverse Event CRF. Some examples of treatment to be recorded are: no action taken (i.e., further observation only); drug of interest dosage adjusted/temporarily interrupted; drug of interest permanently discontinued due to this adverse event; treatment medication introduced or adjusted; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged.

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 drug of interest, the interventions required to treat it, and the outcome.

Information about common adverse effects already known about the medicinal product can be found in the locally available labeling document for the approved indication under evaluation in this study.

3.5.2.2 Serious adverse events

Information about all serious adverse events will be collected and recorded on the Serious Adverse Event Report Form. To ensure patient‘s safety each serious adverse event must also be reported to IQVIA within 24 hours of learning of its occurrence. IQVIA on its turn will promptly inform Recordati. A serious adverse event is an undesirable sign, symptom or medical condition which:

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

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

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- Social reasons and respite care in the absence of any deterioration in the patient’s general 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

Any serious adverse event occurring after the patient has provided informed consent or acknowledged an equivalent document (e.g., written information) as per country regulation and until 28 days after the patient has completed the 3-year observation period or up to 3 months after the last dose of pasireotide s.c. for patients who permanently discontinue pasireotide s.c. prior to completing 3-year observation period must be reported.

Serious adverse events occurring more than 28 days after the patient has completed the 3-year observation period or more than 3 months after pasireotide s.c. discontinuation for patients who permanently discontinue pasireotide s.c. prior to completing the 3-year observation period need only be reported if a relationship to pasireotide s.c. is suspected. Instructions about completing initial and follow-up Serious Adverse Event Report Forms and sending them to IQVIA are given in Section 7.1.1 (Instructions for rapid notification of serious adverse events).

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess and record the relationship of each SAE to pasireotide s.c., complete the SAE Report Form in English, and send the completed, signed form by email within 24 hours to IQVIA Safety Office.

The telephone and telefax number of the contact persons in the local IQVIA Safety Office, 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 person 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, and whether the patient continued or withdrew from study participation.

3.5.2.3 Adverse events of special interest (AESIs)

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

For pasireotide s.c. the following risks are specified as important identified risks: hypocortisolism/cortisol withdrawal syndrome, hyperglycemia, bradycardia, QTc interval prolongation, cholelithiasis, hematological abnormalities, increased liver enzymes, injection site reactions, and gastrointestinal disorders. The following risks are identified as important potential risks for pasireotide s.c.: clinically significant GH/IGF-1 decrease, hypothyroidism, pancreatitis, coagulation abnormalities, hypotension, hypocalcemia, gastrointestinal erosions/bleedings, potential interactions with cyclosporine, drugs metabolized by CYP3A4, bromocriptine, antiarrhythmic medicines and antidiabetics, off-label use in children and other indications, allergic reactions/immunogenicity, and tumor expansion. These important risks represent but are not limited to the AESIs.

Targeted follow-up may be required for the following: hypocortisolism/cortisol withdrawal syndrome, hyperglycemia, and QTc interval prolongation.

3.5.2.4 Pregnancies

Any pregnancy that occurs during study participation should be reported using a Clinical Trial Pregnancy Form. To ensure patient safety each pregnancy must also be reported to IQVIA within 24 hours of learning of its occurrence. IQVIA on its turn will promptly inform Recordati. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities or maternal and newborn complications. Instructions about completing initial and follow-up Clinical Trial Pregnancy Forms and sending them to IQVIA are given in Section 7.1.2.

3.5.2.5 QT prolongation

Pasireotide s.c. has been shown to prolong the QT interval on the ECG in two dedicated healthy volunteer studies. The clinical significance of this prolongation is unknown.

In clinical studies in Cushing's disease patients, QTcF of >500 msec was observed in two out of 201 patients. These episodes were sporadic and of single occurrence with no clinical consequence observed. Episodes of torsade de pointes were not observed either in those studies or in clinical studies in other patient populations.

Pasireotide s.c. should be used with caution and the benefit risk ratio carefully weighed in patients who are at significant risk of developing prolongation of QT, such as those:

- with congenital long QT syndrome.

- with uncontrolled or significant cardiac disease, including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia.
- taking antiarrhythmic medicinal products or other substances that are known to lead to QT prolongation.
- with hypokalemia and/or hypomagnesaemia.

Monitoring for an effect on the QTc interval is advisable and ECG is recommended prior to the start of pasireotide s.c. therapy, one week after the beginning of the treatment and as clinically indicated thereafter. Hypokalaemia and/or hypomagnesaemia must be corrected prior to administration of pasireotide s.c. and should be monitored periodically during therapy.

QTcF/QTcB prolongations > 480 msec will be reported as adverse events in this study.

3.5.2.6 Glucose metabolism

Alterations in blood glucose levels have been frequently reported in healthy volunteers and patients treated with pasireotide. Hyperglycaemia and, less frequently, hypoglycaemia, were observed in subjects participating in clinical studies with pasireotide s.c.

The degree of hyperglycaemia appeared to be higher in patients with pre-diabetic conditions or established diabetes mellitus. During the pivotal study, HbA1c levels increased significantly and stabilized but did not return to the baseline values. Less cases of discontinuation and lower reporting rate of severe AEs due to hyperglycaemia have been reported in patients treated with the dose of 600µg b.i.d.

The development of hyperglycaemia appears to be related to decreases in secretion of insulin (particularly in the post-dose period) and of incretin hormones (i.e. glucagon-like peptide-1 [GLP-1] and glucose-dependent insulinotropic polypeptide [GIP]).

Glycaemic status (fasting plasma glucose/haemoglobin A_{1c} [FPG/HbA_{1c}]) should be assessed prior to starting treatment with pasireotide s.c. FPG/HbA_{1c} monitoring during treatment should follow established guidelines. In addition, monitoring of FPG 4 weeks and HbA1c 3 months after the end of the treatment is recommended. Self-monitoring of blood glucose and/or FPG assessments should be done every week for the first two to three months and periodically thereafter, as clinically appropriate.

If hyperglycemia develops in a patient being treated with pasireotide s.c., the initiation or adjustment of antidiabetic treatment is recommended, following the established treatment guidelines for the management of hyperglycemia. In the majority of patients who developed hyperglycaemia, the condition appeared to be manageable with appropriate antidiabetic therapy. If uncontrolled hyperglycaemia persists despite appropriate medical management, the dose of pasireotide s.c. should be reduced or pasireotide s.c. treatment discontinued.

Cushing's disease patients with poor glycaemic control (as defined by HbA_{1c} values >8% while receiving antidiabetic therapy) may be at higher risk of developing severe hyperglycaemia and associated complications. In patients with poor glycemic control the diabetes management should be intensified prior to initiation and during pasireotide therapy.

3.5.2.7 Cardiac disease

Bradycardia has been reported with the use of pasireotide s.c. Careful monitoring is recommended in patients with cardiac disease and/or risk factors for bradycardia, such as history of clinically significant bradycardia or acute myocardial infarction, high-grade heart block, congestive heart failure (NYHA Class III or IV), unstable angina, sustained ventricular tachycardia, ventricular fibrillation. Dose adjustment of medicinal products such as beta blockers, calcium channel blockers, or medicinal products to control electrolyte balance, may be necessary.

3.5.2.8 Laboratory evaluations

Mild transient elevations in aminotransferases are observed commonly in patients treated with pasireotide. Rare cases of concurrent elevations in ALT greater than 3xULN and bilirubin greater than 2xULN have also been observed.

Monitoring of liver function is recommended prior to treatment with pasireotide s.c. and after one, two, four, eight and twelve weeks during treatment. Thereafter liver function should be monitored as clinically indicated.

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. Therapy with pasireotide s.c. should be discontinued in case the patient develops jaundice or other signs suggestive of clinically significant liver dysfunction, in case of a sustained increase in AST or ALT of 5x ULN or greater, or if ALT elevations greater than 3xULN occur concurrently with bilirubin elevations greater than 2xULN. Following discontinuation of treatment with pasireotide s.c. patients should be monitored until resolution.

As the pharmacological activity of pasireotide s.c. mimics that of somatostatin, inhibition of pituitary hormones other than ACTH cannot be ruled out. Monitoring of pituitary function (e.g. TSH/free T_4, GH/IGF-1) before and periodically during pasireotide s.c. therapy should therefore be considered, as clinically appropriate.

Available data on the following laboratory parameters will be collected in this study:

- AST
- ALT
- Alkaline phosphatase
- γGT
- α-amylase
- Total bilirubin
- WBC
- RBC
- Hemoglobin
- Hematocrit
- Platelets
- Sodium

- Potassium
- Magnesium
- Fasting Plasma Glucose
- HbA1C
- GH
- IGF-1
- TSH
- Free T4
- PT
- APTT

If total bilirubin concentration is increased above 2.0 times upper limit normal (ULN), total bilirubin is recommended to be differentiated into the direct and indirect reacting bilirubin.

All local laboratories contributing to the study should provide the sponsor with a copy of each laboratory's certification and a tabulation of the normal ranges and standard deviations from control values for each of the parameters being evaluated. These laboratory references should be forwarded to the sponsor prior to study start and updated promptly if any information changes during the course of the study.

3.5.2.9 Vital signs

Available systolic and diastolic blood pressure data will be collected in this study. Blood pressure should be measured after the subject has rested in the sitting position for at least 3 minutes and should be assessed using the same arm each time. In addition, the body temperature, heart rate, weight and height should be recorded.

Information about all vital signs must be present in the source documentation at the study site.

3.5.2.10 ECG

Monitoring for an effect on the QTc interval is advisable and ECG is recommended prior to the start of pasireotide s.c. therapy, one week after the beginning of the treatment and as clinically indicated thereafter. Available data of ECG scans, in particular QT values, will be recorded in this study. QTcF/QTcB prolongations > 480 msec have to be reported as adverse events in this study.

3.5.2.11 Gallbladder ultrasound

Cholelithiasis is a recognised adverse reaction associated with long-term use of somatostatin analogues and has frequently been reported in clinical studies with pasireotide s.c. Ultrasonic examination of the gallbladder before and at 6- to 12-month intervals during pasireotide s.c. therapy is therefore recommended. The presence of gallstones in pasireotide s.c.-treated patients is largely asymptomatic; symptomatic stones should be managed according to clinical practice.

3.5.2.12 Concomitant medications including significant non-drug therapies

All concomitant medications and significant non-drug therapies (e.g., surgery, radiation) will be recorded in this study on an ongoing basis. This will also include any information on antidiabetic treatment.

3.5.3 Efficacy assessments

3.5.3.1 Laboratory evaluations

In general UFC is determined by collecting two or three 24-hour urine samples and calculating the mean. However routine site procedures may also only foresee one single urine sample to assess UFC. The frequency of UFC determination will probably vary from the initiation of treatment (when UFC values will be performed more frequently than at monthly interval) as compared to the time after obtaining control.

After obtaining control, at a minimum UFC assessments are recommended to be collected every 6 months.

In addition, the last available UFC value before study entry will be collected on the CRF, only if there is no UFC value available at baseline.

Other biochemical measures of disease activity that will be collected as available in addition to UFC in this study include serum cortisol, serum cortisol after dexamethasone testing, salivary cortisol, plasma ACTH, and fasting serum lipid profile.

3.5.3.2 Clinical signs and symptoms

Assessments collected in this study include blood pressure, weight, body mass index, waist circumference and clinical symptoms of Cushing's disease as available.

3.5.3.3 MRI and other imaging techniques

Available data from MRI scans or other imaging techniques of the tumor will be collected in this study to assess tumor diameter and volume.

3.5.3.4 Quality of Life

Available data from Quality of Life questionnaires (Cushing QoL and EURO QoL) will be collected in this study.

4 Protocol amendments, other changes in study conduct

Any changes to the protocol will be made in the form of an amendment. Changes in conduct of this study are not permitted. Any unforeseen changes in conduct of this study will be recorded in the clinical study report.

5 Data management

5.1 Site monitoring

Before study initiation sponsor personnel or a designated representative will review the protocol with the investigators and their staff. During the study, sponsor personnel or a designated representative may visit the site regularly to assist the site on issues in context with the study. A field monitor will be assessing GCP compliance and progress of enrollment. The site personnel must be available to assist the field monitor.

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 specifically entered in the database for this study must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form or an equivalent document (e.g., written information) as per country regulation signed by the patient (if the patient has to sign off as per country regulation). A signed copy is given to the patient if required by country regulation.

The investigator must give the sponsor personnel or designated representative access to all relevant source documents to confirm their consistency with the database entries.

5.2 Data collection

Designated investigator staff will enter the available patient data (refer to Section 3.5) into the Electronic Case Report Forms (eCRF) using fully validated software that conforms to 21 CFR Part 11 requirements. Designated 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 e-CRFs and, by generating appropriate error messages, allow modification or verification of the entered data by the investigator staff before transfer of data to Recordati (or designated CRO).

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

5.3 Database management and quality control

Data will be entered into the study database by the investigator/study coordinator. Recordati 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 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.

After the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made by joint written agreement between the Head of Biostatistics and Data Management and the Global Therapeutic Area Head.

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

6 Statistical methods

All statistical analysis will be performed under the direction of Recordati personnel. It is planned that the data from all centers that participate in this protocol will be used.

The data will be summarized with respect to demographic and baseline characteristics, safety observations and measurements as well as efficacy assessments. Data will be summarized and displayed by time intervals based visit windows rather than by a strict visit schedule, in order to reflect the nature of this study. Details on definition of time windows will be provided in the Report and Analysis Plan (RAP). Furthermore, for patients who discontinue treatment prior to the 3-year observation period, their safety and efficacy parameters will be reported according to the time window that corresponds to 90 days from the Day of last dose of pasireotide s.c . Continuous variables will be summarized by number of patients, mean, standard deviation, minimum, median and maximum. Categorical variables will be summarized by absolute and relative frequencies. Counts of missing values for both continuous and categorical variables will be reported. Results with and without imputation will be reported.

Baseline assessment refers to the last assessment prior to the patient's first pasireotide s.c. dose recorded after the signing of the informed consent or acknowledging an equivalent document (e.g., written information) as per country regulation. For some assessment this definition maybe expanded to include the first assessment post the first pasireotide s.c. dose recorded after informed consent or an equivalent document (e.g., written information) as per country regulation.

In this study, the first analysis will occur at about 12 months after the first patient enters the study. After this first analysis there will be one analysis on a yearly basis. The final analysis will occur when all patients complete the study. The same analysis will be performed for all analyses time points.

Assessment time points are considered relative to first pasireotide s.c. dose recorded on or after the singing of the informed consent or acknowledging of an equivalent document (e.g., written information) as per country regulation, unless noted otherwise.

In this study there will be two distinct patient cohorts that are based on prior pasireotide s.c. use namely, patients that started the use of pasireotide s.c. at time of study entry (on or after the signing of the informed consent or acknowledging an equivalent document (e.g., written information) as per country regulation) and the cohort of patients that have used pasireotide s.c. prior to study entry. Most of the efficacy and safety analysis will be done by these cohorts, in addition to the analysis by the overall population. Furthermore, if the cohort of patients that have used pasireotide s.c. prior to study entry are heterogeneous or there are sufficient number of patients, selected safety and efficacy analysis will be done by subgroup of patients where the subgroup is based on duration of pasireotide s.c. use prior to study entry.

6.1 Analysis sets

The following analysis sets will be used for statistical analysis and data reporting.

6.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients who have signed informed consent or acknowledged an equivalent document (e.g., written information) as per country regulation and have been treated with pasireotide s.c. after enrolling into the study.

6.1.2 Safety Set

Safety set comprises all 1 patients who have signed informed consent or acknowledged an equivalent document (e.g., written information) as per country regulation and have been treated with pasireotide s.c. after enrolling into the study and with at least one safety assessment.

6.2 Patient demographics/other baseline characteristics

Demographic and other baseline characteristics will be summarized descriptively for the FAS. Categorical data will be summarized by frequency and percentages. Quantitative data will be summarized by the number of patients (n), mean, standard deviation, median, minimum, maximum.

6.3 Treatments (pasireotide s.c., concomitant therapies)

The medication for this study is pasireotide s.c. Prescribing information on the pasireotide s.c. start and stop dates, dose, dose changes and reason for changes. The actual mean daily dose and duration of drug exposure while in the study will be summarized by descriptive statistics and corresponding listing will be presented. Incidence rates by person-time of exposure and incidence rates by person-time of observation with their corresponding 95% confidence interval will be reported.

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

These analyses will be performed on the safety set.

6.4 Primary objective

To document the long-term safety and tolerability profile of pasireotide s.c. when administered as monotherapy or in combination with other therapies in patients with Cushing's disease. The safety set will be used for the analysis of clinical safety data.

6.4.1 Variable

Incidence of pasireotide s.c.-related adverse events and serious adverse events during the 3-year observation period.

6.4.2 Statistical hypothesis, model, and method of analysis

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

The analysis of the primary variable is described in Section 6.5.2.1.

6.4.3 Handling of missing values/censoring/discontinuations

No imputation method will be used to adjust for missing values.

6.5 Secondary objectives

Refer to Section 2.2.

6.5.1 Efficacy evaluation

The secondary efficacy analysis will be performed on the FAS.

The secondary efficacy endpoints are as follows:

- Proportion of patients with a mean UFC ≤ ULN at 1, 3, 6, 12, 24 and 36 months after enrolling into the study
- The absolute and percentage change from baseline in biochemical measures of disease activity (mean UFC, serum cortisol, serum cortisol after dexamethasone testing, salivary cortisol, ACTH and fasting serum lipid profile) over time
- Proportion of patients achieving normalization of biochemical measures of disease activity (serum cortisol, serum cortisol after dexamethasone testing, salivary cortisol, and ACTH) over time, where normalization refers to being within the upper and lower limit of normal ranges
- The absolute and percentage change from baseline in clinical signs and symptoms (blood pressure, body weight, body mass index, waist circumference) over time
- The proportion of patients with favorable shift from baseline in clinical symptoms of Cushing's disease over time
- The change from the last dose of pasireotide s.c. to 3 months after permanent discontinuation of pasireotide s.c. for patients that discontinue pasireotide s.c. prior to completing the 3-year observation period. This change will be evaluated for all available continuous safety and efficacy parameters
- The absolute and percentage change from baseline in tumor size over time
- The absolute and percentage change from baseline in patient reported outcome questionnaires (Cushing QoL and EURO QoL) over time

6.5.1.1 Proportion of patients with mUFC ≤ ULN

In general UFC is determined by collecting two or three 24-hour urine samples and calculating the mean. However, routinely some sites may also use only one single urine sample to assess UFC. In this study, if there are two or three assessments of UFC within 24-hours, then mean UFC refers to mean of these UFC assessments. In contrast, if what is available is just one assessment, then mean UFC refers to this single assessment.At each specified visit window (month 1, 3, 6, 12, 24 and 36) the number and percentage of patients with mean UFC ≤ ULN will be presented together with corresponding exact 95% confidence interval (CI).

6.5.1.2 Absolute and percentage change from baseline secondary efficacy endpoints

For each visit window, the absolute and percentage change from baseline values will be summarized by number of patients, mean, standard deviation, median, minimum, maximum. Furthermore, depending on the distribution of the data, the central tendency of the data will be summarized by generating a 95% CI for the mean absolute change and mean percentage change from baseline values, for approximately normally distributed data. In contrast, for heavily skewed data the 95% CI for the median might be generated, or the mean of the log transformed data might be analyzed as described for approximately normally distributed data.

6.5.1.3 Absolute change between the last assessment on drug and 3 months later for continuous secondary efficacy endpoints

For each efficacy assessment (see Section 6.5.1 for the list of assessments), if sufficient patients have assessments 3-months after permanent pasireotide s.c. discontinuation, the absolute change from the last assessment while on pasireotide s.c. to three months after drug discontinuation, will be similarly summarized.

6.5.1.4 Normalization of biochemical measures of disease activity and clinical symptoms of Cushing's disease

For each appropriately defined visit window, the number and percentage of patients with normalization of biochemical measures of disease activity will be presented together with corresponding exact 95% confidence interval (CI).

For each variable associated with clinical symptoms of Cushing's diseases, and for each appropriately defined visit window, the number and percentage of patients with favorable shift from baseline will be presented together with corresponding exact 95% CI. Furthermore, shift tables from baseline to certain visit windows might be presented.

6.5.1.5 Handling of missing data

For the analysis of these efficacy endpoints, for missing values, Mixed Effects Repeated Measured Model will be employed to assess the longitudinal changes in efficacy parameters. In addition, sensitivity analyses will be performed to assess the robustness of the efficacy findings.

The imputation method as well as sensitivity analyses will be specified in the RAP.

6.5.2 Safety evaluation

For all safety analyses, the safety set will be used. Safety analysis will be stratified by incident or prevalent use of the drug.

Safety and tolerability assessments include AEs, vital signs, blood pressure, heart rate, body temperature, blood glucose (fasting plasma glucose, HemoglobinA1c), hormones (GH,IGF-1, TSH/free T_4), liver enzymes (AST, ALT, alkaline phosphatase, γGT, total bilirubin), hematology, electrolytes, immunological events (e.g., allergic reactions: rash, pruritus, injection site reactions), gallbladder ultrasound and ECGs.

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

1. on-treatment period: from day of enrolling into the study to 28 days after last dose of pasireotide s.c.-
2. post-treatment period: starting at day 28+1 after last dose of pasireotide s.c.

Safety data will be largely collected for the on-treatment period.

For continuous safety variables, the change from the last dose of pasireotide s.c. to 3 months after permanent discontinuation of pasireotide s.c. for patients that discontinue pasireotide s.c. prior to completing the 3-year observation period will be summarized.

6.5.2.1 Adverse events

The incidence of on-treatment adverse events will be summarized by system organ class and preferred term using the MedDRA dictionary. A similar table will also be produced for the post-treatment period.

Similar summary will also be provided for AESIs summarized by category and preferred term (according to the risks specified in Section 3.5.2.3).

The primary objective of this study, the number and percentage of patients having any pasireotide s.c.-related adverse event and serious adverse event will also be separately summarized by system organ class and preferred term using the MedDRA dictionary for the on-treatment period.

AE listing will be generated for the overall AEs, pasireotide s.c. related AEs, SAEs, AESIs and deaths. These listings will cover both events that occur during the on-treatment and post-treatment period however, events that occur during the post-treatment period will be flagged.

6.5.2.2 Laboratory evaluations

All laboratory values will be converted into SI units.

The frequency of laboratory abnormalities will be summarized for each parameter. Laboratory data will also be summarized via shift tables. A listing of laboratory values will be provided by laboratory parameter, patient and visit window. No imputation for missing values will be done for laboratory variables and they will be identified as missing.

6.5.2.3 Other safety data

Available data from other tests (e.g. vital signs, glucose metabolism evaluations, ECG, and gallbladder imaging) will be summarized descriptively by visit window. Shift tables will be provided as appropriate. No imputation for missing values will be done for those variables and they will be identified as missing.

6.5.3 Subgroup analysis

Selected efficacy and safety analysis outlined in the Section 6.5.1 and Section 6.5.2 will be produced for patients treated with monotherapy pasireotide s.c., and those treated in combination with other therapies, separately. If there is a sufficiently large number of patients treated with a specific combination therapy, there might be a separate analysis for this subgroup of patients.

If the cohort of patients that have used pasireotide s.c. prior to study entry are heterogeneous or there are sufficient number of patients, selected safety and efficacy analysis will be done by subgroup of patients where the subgroup is based on duration of pasireotide s.c. use prior to study entry.

Furthermore, selected efficacy and safety analysis outlined in Section 6.4.1, Section 6.5.1 and Section 6.5.2 will also be repeated for subgroup of patients coming from German Sites and other countries as requested.

Additional subgroup analysis may be defined in the report analysis plan (RAP).

6.6 Interim analyses

An interim analysis has been requested by Health Authorities and is planned about 12 months after study start and yearly thereafter until study end. The interim analyses will include the analyses described in Section 6 above.

Furthermore, additional analyses – including of local and/or regional data - may be performed for regulatory purpose or publication purpose. Details will be specified in the statistical analysis plan. The final analysis will occur when all patients complete the study.

6.7 Sample size and power considerations

The sample size for this study is not based on statistical considerations. It is anticipated that up to approximately 100 sites in about 35 countries will participate in the study. The study will enroll a minimum of 100 patients up to a maximum of 200 patients. The actual sample size may differ from this planned number.

7 Procedures and instructions

7.1 Procedures and instructions

7.1.1 Instructions for rapid notification of serious adverse events

7.1.1.1 Reporting responsibility

Each serious adverse event must be reported by the investigator to IQVIA within 24 hours of learning of its occurrence, even if it is not felt to be treatment-related. Follow-up information about a previously reported serious adverse event must also be reported within 24 hours of the investigator receiving it. If the serious adverse event is not previously documented (new occurrence) and is thought to be related to pasireotide s.c.,IQVIA/Recordati may urgently require further information from the investigator for Health Authority reporting. Recordati may need to issue an investigator notification, to inform all investigators involved in any study with pasireotide s.c. that this serious adverse event has been reported.

7.1.1.2 Reporting procedures

The investigator must complete the Serious Adverse Event Report Form in English, assess the relationship to pasireotide s.c. and send the completed, signed form by fax within 24 hours to

the IQVIA. The original copy of the Serious Adverse Event Form and the fax confirmation sheet must be kept at the study site

Follow-up information is sent to the same person sent the original Serious Adverse Event Form. A new serious adverse event form is sent, stating that this is a follow-up to the previously reported serious adverse event 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. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or discontinued study participation. The form and fax confirmation sheet must be retained. Refer to the IQVIA guidelines as needed for instructions for completing the Serious Adverse Event Form.

7.1.1.3 Contact persons and numbers

The telephone and telefax numbers of the contact persons in the IQVIA safety office, are listed in the investigator folder provided to each site.

7.1.2 Instructions for rapid notification of pregnancies

Each pregnancy that started during the study must be reported by the investigator to IQVIA within 24 hours of learning of its occurrence. Pregnancies and pregnancy follow-up should be reported on the Clinical Trial Pregnancy Form but any serious adverse event experienced during pregnancy must be reported on the Serious Adverse Event Report Form. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, the presence or absence of any congenital abnormalities or birth defects, maternal or newborn complications and their relation to pasireotide s.c. Follow-up on pregnancies will be done on a quarterly basis.

7.2 Administrative procedures

7.2.1 Changes to the protocol

Any change or addition to this protocol requires a written protocol amendment that must be approved by Recordati and the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study, require additional approval by the IRB/IEC/REB of all centers unless not required by country regulation, and, in some countries, by the regulatory authority. A copy of the written approval of the IRB/IEC/REB, which becomes part of the protocol, must be given to the IQVIA monitor unless not required by country regulation.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or by Recordati in the interests of preserving the safety of all subjects included in the study. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented by him/her for safety reasons Recordati should be notified and the IRB/IEC/REB at the center should be informed within 10 working days.

Amendments affecting only administrative aspects of this study do not require formal protocol amendments or IRB/IEC/REB approval but the IRB/IEC/REB of each center must be kept informed of such administrative changes unless not required by country regulation. Examples of administrative changes not requiring formal protocol amendments and IRB/IEC/REB

approval that can be treated as administrative amendments include e.g., changes in the staff used to monitor this study (e.g. Recordati staff versus a CRO).

7.2.2 Monitoring procedures

Before study initiation_Recordati personnel or a designated representative will review the protocol and corresponding documents with the investigators and their staff. During this study a field monitor may visit the site to check the completeness of patient records, the accuracy of entries in the database, the adherence to the protocol and to Good Clinical Practice. Key study personnel must be available to assist the field monitor during these visits.

The investigator must give the monitor access to relevant hospital or clinical records, to confirm their consistency with the entries in the database. No information in these records about the identity of the subjects will leave the study center. Recordati monitoring standards require full verification for the presence of informed consent or equivalent document (e.g., written information) as per country regulation, adherence to the inclusion/exclusion criteria, documentation of serious adverse events and the recording of primary efficacy and safety variables if available. Additional checks of the consistency of the source data with the data entered in the database are performed according to the study-specific monitoring plan.

7.2.3 Recording of data and retention of documents

The investigator must complete the data entry forms in the database. All entries to the data forms must be made as described in completion guidelines or as instructed by Recordati personnel or the designated representative at study initiation.

Data on subjects collected during the study will be documented in an anonymous fashion and the subject will only be identified by the subject number. If, as an exception, it is necessary for safety or regulatory reasons to identify the subject, both Recordati and the investigator are bound to keep this information confidential.

The investigator must maintain source documents for each patient in this study, consisting of all demographic and medical information, including laboratory data, electrocardiograms, etc, and keep one original version of the signed informed consent form or an equivalent document (e.g., written information) as per country regulation. All information on data report forms must be traceable to these source documents in the patient's file. Data without a written or electronic record will be defined before study start and will be recorded directly on the data report forms, which will be documented as being the source data.

Essential documents, as listed below, must be retained by the investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). Recordati will notify the investigator(s)/institution(s) when the study-related records are no longer required. The investigator agrees to adhere to the document retention procedures by signing the protocol. Essential documents include:

1. IRB/IEC/REB approvals for the study protocol and all amendments unless not required as per country regulation
2. all source documents and laboratory records
3. CRF copies (paper copies or electronic copies on a CDROM, depending on the study)

4. patients' informed consent forms (with study number and title of study) or equivalent document (e.g., written information) as per country regulation
5. FDA form 1572 (as required)
6. any other pertinent study document.

7.2.4 Auditing procedures

Recordati will delegate some study-related activities, including monitoring, to CROs having in place a Quality Management System to ensure compliance with written Standard Operating Procedures as well as applicable guidelines. Recordati will maintain the oversight of any study-related duties, functions and delegated activities. Audits can be performed at CRO offices and at sites.

A regulatory authority may also wish to conduct an inspection (during the study or even after its completion). If an inspection is requested by a regulatory authority, the investigator must inform Recordati immediately that this request has been made.

7.2.5 Publication of results

EU mandated Non-interventional (NIS) Post Approval Safety Studies (PASS) or NIS PASS with 1 site in EU will be registered on ENCePP (//www.encepp.eu/), including the redacted protocol, before first patient first visit (FPFV) for prospective studies or start of data collection for retrospective studies. Results of these studies (redacted CSR) will be made publicly available on ENCePP website within 1 year of study completion (last patient last visit, LPLV) for studies in adult patients, within 6 months of LPLV for studies in pediatric patients, and 1 year post end of data collection for retrospective studies.

According to Recordati policy, authors of publication will not receive remuneration for their writing of a publication, either directly from Recordati or through the professional medical writing agency. Author(s) may be requested to present poster or oral presentation at scientific congress; however, there will be no honorarium provided for such presentations.

7.2.6 Disclosure and confidentiality

By signing the protocol, the investigator agrees to keep all information provided by Recordati in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents provided by Recordati (protocols, and other material) will be stored appropriately to ensure their confidentiality. The information provided by Recordati to the investigator may not be disclosed to others without direct written authorization from Recordati-except to the extent necessary to obtain informed consent or acknowledgement of an equivalent document (e.g., written information) as per country regulation from patients who wish to participate in the study.

7.2.7 Discontinuation of study

Recordati reserves the right to discontinue any study under the conditions specified in the clinical study agreement.

7.3 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and the principles of Good Clinical Practice, as described in Recordati-standard operating procedures and:

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

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

7.3.1 Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed informed consent form or an equivalent document (e.g., written information) as per country regulation and other information to subjects, must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) unless not required by country regulation. A signed and dated statement that the protocol and informed consent or equivalent document (e.g., written information) as per country regulation have been approved by the IRB/IEC/REB (unless not required by country regulation) must be given to Recordati before study initiation. The name and occupation of the chairman and the members of the IRB/IEC/REB must be supplied to Recordati. Any amendments to the protocol, other than administrative ones, must be approved by this committee unless not required by country regulation.

7.3.2 Informed consent

The investigator must explain to each subject (or legally authorized representative) the nature of this study, its purpose, the procedures involved, and the expected duration. Each subject must be informed that participation in this study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent or an equivalent document (e.g., written information) as per country regulation will not affect his/her subsequent medical treatment or relationship with the treating investigator.

This informed consent or an equivalent document (e.g., written information) as per country regulation should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating or acknowledging it otherwise as per country regulation, and should be given a copy of the signed document or an acknowledged equivalent document (e.g., written information) if this is required by country regulation. If the subject cannot read or sign the documents or acknowledge it otherwise as per country regulation, oral presentation may be made or signature/other acknowledgement as per country regulation given by the subject's legally appointed

representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained or acknowledgement of an equivalent document (e.g., written information) has been collected as per country regulation.

The informed consent form or an equivalent document (e.g., written information) as per country regulation is considered to be part of the protocol, and must be submitted by the investigator with it for IRB/IEC/REB approval unless not required by country regulation. Recordati-supplies a proposed informed consent form, which complies with regulatory requirements and is considered appropriate for the study. Any changes to the proposed consent form or an equivalent document (e.g., written information) as per country regulation suggested by the Investigator must be agreed to by Recordati before submission to the IRB/IEC/REB unless not required by country regulation, and a copy of the approved version must be provided to the IQVIA monitor after IRB/IEC/REB approval unless not required by country regulation.

7.3.3 Declaration of Helsinki

The investigator must conduct the study in accordance with the principles of the Declaration of Helsinki. Copies of the Declaration of Helsinki and amendments will be provided upon request or can be accessed via the website of the World Medical Association at //wma.net/e/policy/17-c_e.html

8 References (available upon request)

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