RECORDATI AG, Rare Diseases Branch

LCI699-RECAG-NI-0596

A RETROSPECTIVE OBSERVATIONAL STUDY TO EVALUATE THESAFETY AND EFFECTIVENESS OF OSILODROSTAT FOR THE TREATMENT OF NON-CUSHING'S DISEASE CUSHING'S SYNDROME (LINC7 STUDY)

Statistical Analysis Plan

Version: <Final v4.0>

Parexel Project Number: 273637

SPONSOR SIGNATURE PAGE

Approved by:

_____	_____
Alessandro Antonellini Head of Statistics and Biometrics Recordati AG	30 October 2023

PAREXEL SIGNATURE PAGE

Signatures below confirm that the Statistical Analysis Plan was developed in accordance with SOP-GDO-WW-019 and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

	Signatory
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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
0.5	[12 Dec 2022]	New document
1.0	[12 May 2023]	Update for protocol amendment
2.0	[19 July 2023]	Update for mUFC definition and the requests by OSE
3.0	[24 Oct 2023]	Addition of population and analyses
4.0	[30 Oct 2023]	Update for exposure data analysis and further clarification of on-treatment population

LIST OF ABBREVIATIONS

Abbreviation / Acronym	Definition / Expansion
ACTH	Adrenocorticotropic hormone
AE	Adverse Event
AESI	Adverse Events of Special Interest
BL	Baseline
CD	Cushing's Disease
CRF	Case Report Form
CRH	Corticotropin-releasing hormone
CRO	Contract Research Organisation
CS	Cushing's Syndrome
CT	Computed tomography
DCF	Data Clarification Form
DMP	Data Management Plan
DVS	Data Validation Specification
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FSH	Follicle Stimulating Hormone
GPP	Good Pharmacoepidemiology Practices
HbA1C	Glycated Haemoglobin
HCP	Health Care Providers
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intention to Treat
LH	Luteinizing Hormone
LTF	Loss to Follow-Up
MedDRA	Medical Dictionary for Regulatory Activities
NOL	No Objection Letter
PT	Preferred Term

Abbreviation / Acronym	Definition / Expansion
QA	Quality Assurance
SAP	Statistical Analysis Plan
SD	Standard Deviation
SMP	Site Management Plan
sNDA	Supplemental New Drug Application
SOC	System Organ Class
TEAE	Treatment-emergent adverse events
TFL	Tables, Figures, Listings
UFC	Urinary free cortisol
ULN	Upper Limit Normal
WHO	World Health Organization
WK	Week

1 INTRODUCTION

Isturisa® (osilodrostat), an orphan medicine, was approved by the European Union (EU) on 9 January 2020 for endogenous Cushing's Syndrome (CS), and by the United States Food Drug Administration (FDA) on 6 March 2020 for the treatment of Cushing's Disease (CD). Prior to approval and commercialization of osilodrostat in the EU, greater than 50 patients with CS had already been initiated on osilodrostat under the April 2019 French Autorisation Temporaire d'Utilisation (ATU) scheme.

Recordati proposes an FDA label expansion for osilodrostat to include CS. This study therefore intends to evaluate the safety and effectiveness of osilodrostat for the treatment of non-CD CS patients in support of an FDA supplemental New Drug Application (sNDA).

This SAP is based upon the following study documents:

- Study Protocol, Version 2.0 (April 18, 2023)
- Electronic Case Report Design Specification (eCRF), Version 2.0 (January 11, 2023)

2 STUDY OBJECTIVES

The protocol specified study objectives are listed below-

2.1 Primary Objective(s)

- To evaluate the effectiveness of osilodrostat in the treatment of non-Cushing's Disease (CD) Cushing's Syndrome (CS)

2.2 Secondary Objective(s)

- To assess the long-term effects of osilodrostat in the treatment of non-CD Cushing's Syndrome (CS)
- To assess the change in biochemical variables associated with osilodrostat treatment in non-CD CS patients.
- To assess actual and change in clinical outcomes associated with osilodrostat treatment in non-CD CS patients.
- To characterize initiating doses, up- and down-titration regimens for non-CD CS patients treated with osilodrostat.
- To estimate the incidence of overall treatment-emergent adverse events (TEAEs) and adverse events of special interest (AESI) for non-CD CS patients treated with osilodrostat.

2.3 Exploratory Objective(s)

- To assess change in late night salivary cortisol level from baseline to various timepoints for non-CD CS patients treated with osilodrostat.

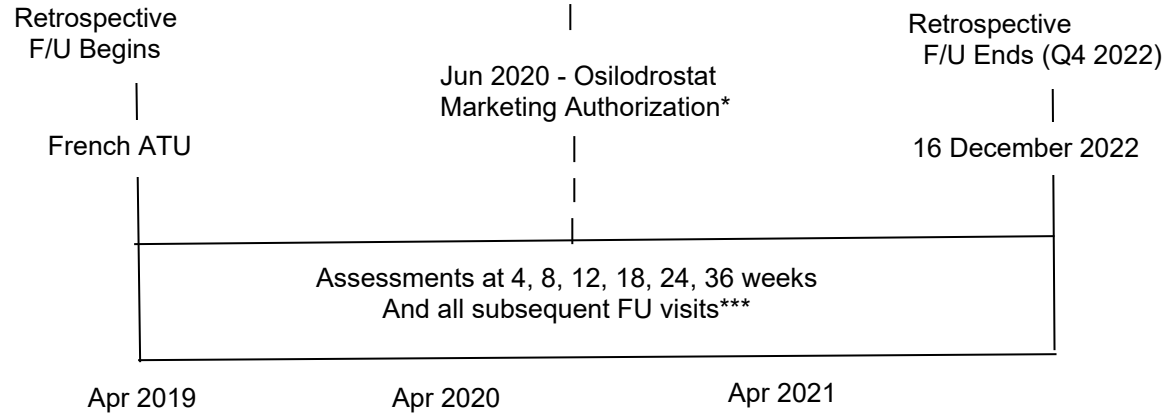
3 STUDY DESIGN

This is a multi-centre, observational, non-comparative, retrospective cohort study designed to evaluate the long-term safety and effectiveness of osilodrostat in non-Cushing's Disease (non-CD) Cushing's Syndrome (CS) patients. Patients treated with oral osilodrostat regardless of the duration of their treatment will be followed retrospectively for up to 36 months after initiating osilodrostat. Follow-up for each patient will be variable, rather than fixed. Using a variable follow-up, rather than a fixed follow-up period for each patient, maximises the person-time of patient follow-up in the study. This methodological approach allows for increased precision of findings compared to a fixed follow-up period because the unit of observation in analyses is person-time accrued aggregately across all eligible patients, rather than a count denominator of patients exposed to osilodrostat.

Participating institutions will be where the past treatment of patients took place using osilodrostat under Autorisation Temporaire d'Utilisation (ATU) and/or as a part of routine clinical practice. Data will be abstracted from patients' existing electronic, or paper institutional medical records collected during the French ATU and/or routine clinical care. Importantly, the historical decisions of health care providers (HCPs) to treat patients with osilodrostat were made purely at the discretion of the treating physicians as discussed with their patients. Thus, there is no relationship between the decision to treat patients with osilodrostat and inclusion in this study.

The study schematic is presented in Figure 1 below and illustrates the dates corresponding to the study's retrospective follow-up period, the French ATU, the latest date an osilodrostat-treated patient is eligible for inclusion in the cohort study, and general timelines.

Figure 1 Study Schematic



***at every 12 weeks until the earlier of LFTU, death, or the end of the retrospective follow-up period or treatment discontinuation

Abbreviations: ATU : Autorisation Temporaire d'Utilisation. ; F/U : Follow Up ; LTFU : Lost to Follow Up,

Clinical practice medical records will be reviewed for all eligible patients who received osilodrostat between April 2019 and the study start date at study sites in France. The study start date was the date the first site was initiated in the study, which was on 16 December 2022. The study will screen all patients at each site who were treated with osilodrostat in France within the frame of the ATU programme prior to commercial availability along with the patients who were treated with commercially available osilodrostat. All patients treated with osilodrostat between April 2019 and the study start date (16 December 2022) will be enrolled in the study. Either the patient has previously signed a general consent for research, or a signed no-

objection letter (NOL) will be requested from the patient if still alive. If patient does not send the NOL back to the investigator, the investigator can document a tacit approval from the patient if there is no response after a month of the first shipment of the NOL and after 3 documented contact attempts. For a deceased patient since his/her past treatment with osilodrostat, access after the investigator has checked that this deceased patient did not leave any written document stating his/her refusal to participate in any scientific research.

Investigators will manually review and abstract clinical information from selected patients' medical records and will enter information into the electronic case report form (eCRF) from the date of initiating Osilodrostat through the follow-up period. All data are safeguarded using industry-best security practices to prevent unlawful disclosure and practices are compliant with Title 21 Part 11 policies of the Code of Federal Regulations. The HIMS software used for EDC purposes include password protection and encryption for all transmitted data. The platform will be approved by Recordati prior to study data abstraction or during site selection procedure.

The follow-up period will be variable, from the start of their osilodrostat onset period until the earlier of loss to follow-up, death, the end of the retrospective follow-up period or treatment discontinuation occurs. The patients with a potential follow-up of at least 12 weeks will be part of the primary analysis. The only patients excluded from the primary efficacy analyses will be the ones who started treatment with osilodrostat less than 12 weeks prior to the end of the abstraction period and are still treated with osilodrostat at the end of the abstraction period. These patients will be included only in the analyses of the secondary and exploratory endpoints including safety. The patients who discontinued treatment for any reason or were lost-to-follow up prior to 12 weeks will be considered non-responders for the primary endpoint. The end of study is defined as the last available assessment after treatment initiation for the last patient.

The timing of data collection is summarized in the Figure 1/Table 1.

Table 1 Data Collection Schedule

	Data Collection Points						
Assessment	**BL [a]**	**Wk 4 [b]**	**Wk 8 [b]**	**Wk 12[b]**	**Wk 18[b]**	**Wk 24[b]**	**Wk 36 and every 12 wks Until death, loss to F/U or end of patient data collection***
Window period		**± 2 wks**	**± 2 wks**	**± 4 wks**	**± 2 wks**	**± 4 wks**	**± 4 wks**
No Objection Letter[c]	X						
Inclusion-Exclusion Criteria	X						
Demographics (age, gender)	X						
BMI	X	X	X	X	X	X	X
Clinical (disease) characteristics including date of diagnosis	X						
Medical and surgical history	X						

CS-Specific Physical Exam Findings (after BMI per every visit)[@]	X	X	X	X	X	X	X
Vital signs (blood pressure)	X	X	X	X	X	X	X
Electrocardiogram	X	X	X	X	X	X	X
Prior cs treatment	X						
Concomitant medications	X	X	X	X	X	X	X
Osilodrostat initiating dose (date)[d]	X	X	X	X	X	X	X
Up- and/or down-titration regimen (date)[d]		X	X	X	X	X	X
Comprehensive Metabolic Panel (CMP&), Complete Blood Count (CBC#), lipids	X	X	X	X	X	X	X
HBA1c	X	X	X	X	X	X	X
Mean urinary free cortisol	X	X	X	X	X	X	X
Morning serum cortisol	X	X	X	X	X	X	X
Plasma Adrenocorticotropic hormone (ACTH), Serum 11-Deoxycortisol, Plasma 11-Deoxycorticosterone, Plasma Aldosterone, Plasma Renin, Total Serum Testosterone or oestradiol (per patient sex), Serum LH, Serum FSH	X	X	X	X	X	X	X
Late night salivary cortisol	X	X	X	X	X	X	X
Adverse event	X	X	X	X	X	X	X
Osilodrostat discontinuation with reason for discontinuation		X	X	X	X	X	X

a. At the time of osilodrostat initiation or the closest value within 2 weeks prior to osilodrostat initiation.

b. Assessments at 4, 8, 12, 18, 24, 36 weeks will be collected, as well as all subsequent follow-up visits (at every 12 weeks until the earlier of loss to follow-up, death, or the end of the retrospective follow-up period or treatment discontinuation) under routine clinical practice, if available. The assessments which occurred closest to each defined visit should be recorded in the CRF, even if these assessments occurred on different dates.

c. Either the patient has previously signed a general consent for research, or a signed no-objection letter (NOL) will be requested from the patient if still alive. If patient does not send the NOL back to the investigator, the investigator can document a tacit approval from the patient if there is no response after a month of the first shipment of the NOL

and after 3 documented contact attempts. For a deceased patient since his/her past treatment with osilodrostat, access after the investigator has checked that this deceased patient did not leave any written document stating his/her refusal to participate in any scientific research.

d. Osilodrostat initiation dose and up- and/or down-titration regimens (including dates) and reasons for titration will be recorded in the database during the study.

e. All prior medications taken within 6 months prior to the first dose of Osilodrostat must be collected.

f. Baseline mean urinary free cortisol data can be collected within 1 month prior to osilodrostat initiation.

g. Footnote-a is not applicable to the following assessments: prior medications, concomitant medications and mean urinary free cortisol.

*End of data collection may be due to earlier of loss-to-follow-up, death, end of retrospective follow-up period or treatment discontinuation.

#CBC includes WBC, RBC, Haemoglobin, Haematocrit, MCV, MCH, MCHC, RDW, Platelet Count, MPV and Differential (Absolute and Percent - Neutrophils, Lymphocytes, Monocytes, Eosinophils, and Basophils).

&CMP includes Albumin, Alkaline Phosphatase, ALT, AST, Calcium, Carbon Dioxide, Chloride, Creatinine with GFR Estimated, Glucose, Potassium, Sodium, Total Bilirubin, Total Protein, (Blood) Urea Nitrogen.

@ For list of CS-specific examination findings, please refer to protocol section 8.3.2.

As this is a descriptive study, the effectiveness and safety endpoints will be summarized descriptively. No formal statistical hypothesis testing will be performed.

Data from an approximately 100 patients meeting the inclusion/exclusion criteria in France will be collected.

3.1 Identification of Analysis Population

Patients will be entered into this study only if they meet all of the following inclusion criteria and none of the following exclusion criteria:

Inclusion criteria:

1) Male and female patients ≥18 years old with diagnosis of CS, except for CD (i.e., an aetiology of adrenal adenoma, adrenocortical carcinoma, adrenal hyperplasia, or ectopic adrenocorticotropic hormone secretion). Patients should have a contemporaneously documented diagnosis of CS as per effective guidelines.

2) Patients treated with osilodrostat between April 2019 and study start date (16 December 2022) as part of ATU programme or commercialisation.

Exclusion criteria:

1) Patients who participated in an interventional clinical trial anytime during the study period.

2) Patients with Pseudo-Cushing's syndrome, cyclic CS, or iatrogenic CS.

As this is a retrospective, non-interventional study, no specific withdrawal and replacement criteria are specified.

3.2 Enrolled Population

All participants treated with osilodrostat between April 2019 and the study start date (16 December 2022), meeting the inclusion/exclusion criteria and for whom authorizations for getting access to the medical data have been ensured, through the existence of a signed general consent, or requesting a signed NOL, or fulfilling the conditions of a tacit approval or no written document stating they refused any participation to scientific research, will be included.

3.3 Primary Analysis Population

ITT Population

The Intent-to-treat population (ITT) consists of all enrolled participants who, have met all inclusion/exclusion criteria and have received osilodrostat treatment for non-CD CS, with a potential follow-up of at least 12 weeks. The only patients excluded from the primary efficacy analyses will be the ones who started treatment with osilodrostat less than 12 weeks prior to the end of the abstraction period and are still treated with osilodrostat at the end of the abstraction period. These patients will be included only in the analyses of the secondary and exploratory endpoints including safety.

All effectiveness analysis will be performed on the ITT population.

Modified ITT Population

This observational study is collecting data from an extended population of patients treated with osilodrostat in Cushing's syndrome in different conditions impacting in the study objectives. Therefore, to allow a better evaluation of the primary objective an additional population has been set.

The Modified ITT population consists of all participants as per the ITT excluding also the patients which for any reasons except for safety reasons did not collect the mean UFC at 12 weeks.

All effectiveness analyses will be performed on the modified ITT population as well.

Modified ITT (mITT) Patient Identification Data Review Process

Step 1. Statistical programmer programs to create excel file, which is a list of patients who will be excluded from ITT population due to lack of mUFC data at week 12. Send this excel file to DML.

Step 2. Based on the list of patients in above excel file, DM team will track all the possible reasons why patients did not have mUFC data at week 12 for each patient.

Step 3. Get the information of reasons for no mUFC data at week 12 from DML, draft data review report.

Step 4. Send the drafted data review report to Recordati for review.

Step 5. Get the review comments from Recordati, discuss the review comments in comments resolution meeting.

The above data review process will also be applied to the missing mUFC data at the baseline.

On-Treatment Population

The On-Treatment population consists of all participants while they are taking osilodrostat at a defined timepoint or period.

- In circumstances where end of treatment date is missing and patient did not change to 0mg prior to end of study, the end of study date will be considered as end of treatment date if end of study reasons were due to adverse event, death, osilodrostat permanently discontinued, administrative reasons (no data reported), end of retrospective follow-up period.
- For cases where last recorded dose was changed to 0mg prior to the end of study, then the date when dose changed to 0mg will be considered as the last date of exposure (i.e., end of treatment date).

Safety Population

The Safety population consists of all participants who receive at least one dose of osilodrostat.

Safety analysis will be performed on the Safety population.

Decisions regarding the exclusion of participants and/or participant data from analyses will be made prior to the Database lock (DBL) during the data review meeting and will be documented and approved by Recordati.

The number and percentage of patients included and excluded from each analysis population, along with reasons for exclusion, will be summarized.

A listing of participants included in each analysis population will also be provided. Participants exclusion from analysis sets will be listed with reasons for exclusions.

3.4 Study Groups/Cohorts

This is retrospective, observational single-cohort study with up to 36 months of retrospective real-world data review period.

3.5 Definitions of Subgroup Indicators

The following subgroup analyses will be performed.

Type of interventions

The participants will be classified according to the interventions they received:

1) ***Tx naïve***: All patients who were treated with Osilodrostat as monotherapy that were not taking any medical therapy for Cushing's syndrome prior to the start of Osilodrostat (limited to somatostatin analogues, dopaminergic medications, and steroidogenesis inhibitors)
2) ***Switch group***: All patients who were treated with Osilodrostat as monotherapy but were taking any medical therapy for Cushing's syndrome and discontinued these prior to the start of Osilodrostat.
3) ***Combination Tx***: All patients treated with both Osilodrostat and any medical therapy for Cushing's syndrome.

Method of Osilodrostat use/ titration

The participants will be classified as follows:

1) ***Block-and-replace:*** Patients who are taking glucocorticoids as concomitant medication less than 2 weeks after initial Osilodrostat.
2) ***Initial titration followed by block-and-replace:*** Patients who initiated Osilodrostat and after at least 2 weeks, started taking glucocorticoids as concomitant medication.
3) ***Titration only***: Patients who did not take glucocorticoids as concomitant medications while taking osilodrostat.

Reason for Osilodrostat use

1) ***Short-term use in preparation for surgery***: Patients who took Osilodrostat for < 12 weeks had a surgical procedure to treat Cushing's syndrome and were not restarted on Osilodrostat.
2) ***Chronic use***: All other patients

Type of non-CD Cushing Syndrome

1) ***ACTH-dependent CS***: Patients classified as "Ectopic Adrenocorticotropic Hormone Secretion" in the "CS Disease Causation".
2) ***Adrenal CS:*** Patients with "Adrenal Adenoma", "Adrenocortical Carcinoma" in the "CS Disease Causation".
3) ***Unclassified***: "Adrenal hyperplasia" and "Other" in the "CS Disease Causation".

3.6 Study Endpoints

3.6.1 Primary Endpoint

The primary endpoint is:

a) Number and proportion of participants with mean urinary free cortisol (mUFC) ≤ upper limit of normal (ULN) at 12 weeks.

3.6.2 Secondary (Supportive) Endpoints

The secondary endpoints are:

a) Proportion of patients with mUFC ⩽ ULN at weeks 24, 36 and every 12 weeks until the earlier of loss to follow-up, death, or the end of the retrospective follow-up period or treatment.
b) Change from baseline for biochemical variables to Week 4, 8, 12, 18, 24, 36, and to every 12 weeks until the earlier of loss to follow-up, death, or the end of the retrospective follow-up period or treatment.
c) Actual and percent Change in BMI, ECG, blood pressure, metabolic, biochemical, and hormone levels from baseline for clinical outcomes to Week 4, 8, 12, 18, 24, 36, and to every 12 weeks until the earlier of loss to follow-up, death, or the end of the retrospective follow-up period or treatment discontinuation
d) Change from initial dose.
e) Proportion of participants who experienced TEAE and AESI

f) Change from baseline of measures of cortisol levels (mUFC, salivary cortisol and morning serum cortisol expressed as x-fold the ULN) to Week 4, 8, 12, 18, 24, 36, and to every 12 weeks until the earlier of loss to follow-up, death, or the end of the retrospective follow-up period or treatment.
g) Partial responders (defined as patients with a ≥50% reduction from baseline, but still >ULN) for measures of cortisol levels (mUFC, salivary cortisol and morning serum and a combination of the 3 measures) to Week 4, 8, 12, 18, 24, 36, and to every 12 weeks until the earlier of loss to follow-up, death, or the end of the retrospective follow-up period or treatment discontinuation.
h) Complete or partial responders: Proportion of participants with normalization of cortisol levels or a partial response: for cortisol levels (mUFC, salivary cortisol and morning serum and combination of the 3 measures) to Week 4, 8, 12, 18, 24, 36, and to every 12 weeks until the earlier of loss to follow-up, death, or the end of the retrospective follow-up period or treatment discontinuation.
i) Composite of normalization cortisol measures at week 12: Patients with W12 mUFC ≤ ULN, or W 12 salivary cortisol ≤ ULN (if w12 mUFC is missing), or W 12 serum cortisol ≤ ULN (if W12 mUFC and salivary cortisol are missing)

3.6.3 Exploratory endpoint(s)

The exploratory effectiveness endpoint is:

a) Proportion of participants with normal late night salivary cortisol at Week 4, 8, 12, 18, 24, 36, and at every 12 weeks until the earlier of loss to follow-up, death, or the end of the retrospective follow-up period or treatment discontinuation
b) On-treatment analysis of cortisol levels
    a. Normalization of cortisol measures at Week 4, 8, 12, 18, 24, 36, and at every 12 weeks until the earlier of loss to follow-up, death, or the end of the retrospective follow-up period or treatment discontinuation (mUFC, salivary cortisol and serum cortisol and a combination of the 3 measures). Participants with normal values at baseline would not enter in this analisis.
    b. Composite of normalization of week 12 cortisol measures: For patients taking Osilodrostat on week 12 (mUFC, salivary cortisol and morning serum and a combination of the 3 measures).
    c. Normalization to the last on treatment cortisol measures (mUFC, salivary cortisol and morning serum and a combination of the 3 measures).
    d. Patients with normalization of the majority of cortisol measures: Defined as patients on Osilodrostat treatment that have multiple measures of cortisol levels over time and have >50% of these measures ≤ ULN (mUFC, salivary cortisol and morning serum and a combination of the 3 measures).
    e. Change from baseline of measures cortisol level: Defined as the change from baseline in measures of cortisol levels including only patients receiving Osilodrostat the time-point (expressed by the unit and bx nfold ULN) for mUFC, salivary cortisol and morning serum and a combination of the 3 measures.
    f. Complete or partial responders: The proportion of patients with normalization of cortisol levels or a ≥50% reduction from baseline for patients receiving Osilodrostat at week 4, 8, 12, 18, 24, 36, and at every 12 weeks until the earlier of loss to follow-up, death, or the end of the retrospective follow-up period or treatment discontinuation (mUFC, salivary cortisol and morning serum and a combination of the 3 measures).
    g. Waterfall plot figures of change in measures of cortisol level from baseline to last on treatment expressed as n-fold ULN (mUFC, salivary cortisol and morning serum and a combination of the 3 measures) grouped by duration of exposure to osilodrostat (0 to 4 weeks, 5 to 8 weeks, 9 to 12 weeks, 13 to 24 weeks, >24 weeks).

4 DATA SOURCE

The primary data source for this study will be the existing electronic medical records stored in the hospital information management systems (HIMS) and laboratory information management systems (LIMS) at the investigative sites. Also, where applicable, data will be captured from paper medical records. The Investigator or authorized medical staff will record clinical and treatment data from participants' medical files into the eCRF.

Participant identification period:

Participants meeting eligibility criteria will be retrospectively identified and included in the study by site investigators based on a review of medical records at site. Site policies and local regulations regarding participant consent (NOL) will be followed. All eligible participants identified at a site between April 2019 and study start date and consenting to be part of the study will be included.

Index date:

The index date is the first dose of osilodrostat (index treatment).

5 STATISTICAL METHODS

5.1 Data Quality Assurance

All tables, figures, and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard PAREXEL procedures for analysis and reporting.

The data for the planned analysis will be quality controlled as per applicable PAREXEL standard operating procedures. The data extraction will be set to an appropriate date so that all data cleaning activities which include any corrections are taken care of.

5.2 General Presentation Considerations

All report outputs will be produced using SAS® version 9.4 or a later version in a secure and validated environment. All report outputs will be provided to the Sponsor in a single Microsoft Word document. Medical history, procedural/surgical history, and Adverse Events (AE) will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). The frequency count and percentage of participants will be summarized according to the coded terms of system organ class (SOC) and preferred term. Participant-wise data listing will be provided.

Using the World Health Organization Drug Dictionary (WHO DD), prior and concomitant medications will be tabulated by drug classification, preferred drug name and study group.

Continuous data will be summarized in terms of the descriptive statistics, number of observations (n), mean and SE of mean or 95% CI of mean (as appropriate), SD, median and associated 95% CI of median (as appropriate), minimum, and maximum, unless otherwise stated.

Continuous data that are expected to be skewed and will be presented in terms of the maximum, upper quartile, median, lower quartile, minimum and number of observations. The mean, median will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number of participants providing data at the relevant time point (N), frequency counts and percentages.

Time to event endpoints will be summarized in terms of participants providing data, median and quartiles and represented graphically by Kaplan-Meier curves.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using N as the denominator.

Changes from baseline in categorical data will be summarized using shift tables where appropriate.

Confidence intervals will be presented to one more decimal place than the raw data.

95% confidence intervals for proportions will be calculated using the exact (Clopper-Pearson) method, unless stated otherwise.

Baseline is defined as the available value at the time of osilodrostat initiation or the closest value within 2 weeks prior to osilodrostat initiation.

Change from baseline will be calculated as the post-baseline value of interest minus the baseline value. Percent change from baseline is defined as: 100 × [(post-baseline – baseline) / baseline]. If all baseline values are missing for a particular variable, the change from baseline and percent change from baseline will not be calculated.

5.3 Statistical methods

5.3.1 Discussion of Analytical Approaches

The statistical analyses will be performed in accordance with Good Pharmacoepidemiology Practice (GPP) guideline / International Conference on Harmonisation (ICH) E9 guideline and will be based on the pooled data from the individual study sites, unless otherwise stated. The Statistical analysis will be performed by Parexel and reviewed by Recordati.

5.3.2 Analysis of the Primary Endpoint

The mean UFC for a participant at any particular visit is collected in the site. If mean UFC is not available at that visit, the mean UFC will be computed based on two or more individual 24hr UFC specimens at that visit. If there are only one individual 24hr UFC specimen available at that visit, then this one individual 24hr UFC specimen will be considered as mean UFC with the acknowledgement of clinical practice in France where one 24 hours UFC can inform on clinical decision.

The primary endpoint is the number and proportion of participants with mUFC ≤ ULN at 12 weeks will be summarized descriptively along with associated 95% CI. The participants who discontinued treatment prior to 12 weeks for any reason or were lost-to-follow up will be considered non-responders for the primary endpoint. The participants who started treatment with osilodrostat less than 12 weeks prior to the end of the abstraction period and are still treated with osilodrostat at the end of the abstraction period will be excluded from the analysis.

The primary endpoint will be evaluated also on the modified ITT population, in which participants who had any intervention for any reason or condition that would not allow to have a mean UFC evaluation at 12 weeks will be excluded from the analysis. Participants who discontinued prior to 12 weeks due to safety reasons will be considered non -responders.

The summary statistics will include sample size, frequency, percentages, and 95% CI for proportion.

A participant level listing of participants with mUFC will be provided with UFC, ULN, date of assessment, lost to follow up date etc.

5.3.3 Analysis of the Secondary Endpoints

The secondary endpoints will be evaluated as follows:

5.3.3.1 Proportion of participants with mUFC ≤ ULN at weeks 24, 36 and every 12 weeks thereafter

The number and proportion of participants with mUFC ≤ ULN at 24, 36 and every 12 weeks thereafter will be summarized descriptively along with associated 95% CI.

5.3.3.2 Changes from baseline for biochemical variables and clinical outcomes

For changes from baseline for mUFC and morning serum cortisol to Week 4, 8, 12, 18, 24, 36, and to every 12 weeks until the earlier of loss to follow-up, death, or the end of the retrospective follow-up period or treatment discontinuation, descriptive summaries will be provided.

A participant level listing of biochemical variables and clinical outcomes will be provided as per the data collected in eCRF.

5.3.3.3 Changes from baseline for cortisol expressed as n-fold the ULN

For the mUFC will be calculated the ratio of the value divided by the ULN and calculated as change form baseline and reports as n-fold.
This will be applied also to salivary and morning serum cortisol.

For changes from baseline for cortisol to Week 4, 8, 12, 18, 24, 36, and to every 12 weeks until the earlier of loss to follow-up, death, or the end of the retrospective follow-up period or treatment discontinuation, descriptive summaries will be provided.

5.3.3.4 Actual and percent change in BMI, ECG, blood pressure, metabolic, biochemical, and hormone levels from baseline for clinical outcomes

The following variables will be summarized and provided as listing:

BMI, ECG, Blood pressure, CS-specific physical exam findings, Laboratory abnormalities (sodium, potassium, calcium levels, CO2, glucose, Glycated haemoglobin (HBA1c), and hormones (including Plasma ACTH, Serum 11-Deoxycortisol, Plasma 11-Deoxycorticosterone, Plasma Aldosterone, Plasma Renin, Total Serum Testosterone or oestradiol per participant sex, Serum LH, Serum FSH)

For observed values and changes from baseline for above variables to Week 4, 8, 12, 18, 24, 36, and to every 12 weeks until the earlier of loss to follow-up, death, or the end of the retrospective follow-up period or treatment discontinuation, descriptive summaries will be provided.

5.3.3.5 Change from initial dose

The osilodrostat dose and change from initial dose by visits will be summarized using descriptive statistics and displayed graphically.

The actual and planned osilodrostat doses administered and reason for dose change will be listed with UFC information.

5.3.3.6 Partial responder

A partial responder is defined as a participant with 50% reduction from baseline, but still >ULN for measures of cortisol levels.

The number and proportion of partial responders at Week 4, 8, 12, 18, 24, 36, and to every 12 weeks thereafter will be summarized descriptively along with associated 95% CI.
This will be reported for mUFC, salivary cortisol and morning serum cortisol as well as the combination of the 3 measures (any of the measures and reported as “Cortisol”).

5.3.3.7 Complete or partial responder

The number and proportion of complete or partial responders at Week 4, 8, 12, 18, 24, 36, and to every 12 weeks thereafter will be summarized descriptively along with associated 95% CI.
This will be reported for mUFC, salivary cortisol and morning serum cortisol as well as the combination of the 3 measures (any of the measures and reported as “Cortisol”).

5.3.3.8 Normalization

The number and proportion of participants with salivary cortisol ≤ ULN at Week 4, 8, 12, 18, 24, 36, and to every 12 weeks until the earlier of loss to follow-up, death, or the end of the retrospective follow-up period or treatment discontinuation, will be summarized descriptively along with associated 95% CI.
This will be applied also to morning serum cortisol.

Normalization will be evaluated also as frequency of participants with at least 50% of the measures ≤ ULN.
This will be reported for mUFC, salivary cortisol and morning serum cortisol as well as the combination of the 3 measures (any of the measures and reported as “Cortisol”).

5.3.3.9 Composite normalization

The definition of composite normalization is the condition of the value ≤ ULN of any type of cortisol. For any given time point a responder in this composite will be defined a patients with mUFC ≤ ULN, or salivary cortisol ≤ ULN (if mUFC is missing), or serum cortisol ≤ ULN (if mUFC and salivary cortisol are missing)..

The number and proportion of participant achieving composite normalization at 4, 8, 12, 24, 36 and every 12 weeks thereafter will be summarized descriptively along with associated 95% CI.

5.3.3.10 Time to normalization

Time to normalization is the interval between start of osilodrostat administration and time of normalization of cortisol levels.

The participants not reaching the normalization will be censored at the date of the last available cortisol measure.

In the case of the composite analysis the baseline would be the closest measure to the start of osilodrostat among the different cortisol assessments (mUFC, salivary and serum) and the time of normalization is the first occurring among the cortisol measures. Censored dates will be the date of the last available cortisol measure. In case of multiple measures at a timepoint the the definition of composite normalization will be applied.

This will be reported for mUFC, salivary cortisol and morning serum cortisol as well as the combination of the 3 measures (any of the measures and reported as “Cortisol”).
The number and proportion of events and censored values will be presented together with median time, (95% CI), quartiles, minimum and maximum and Kaplan-Meier curves will be produced for analysis.

5.3.3.11 Proportion of participants who experienced TEAE and AESI

A treatment-emergent adverse event (TEAE) is defined as an AE that begins or that worsens in severity after at least one dose of osilodrostat has been administered. The start date of adverse events will be compared with date of first dose of osilodrostat and the date of the earlier of loss to follow-up, death, the end of the retrospective follow-up period or treatment discontinuation occurs, whichever is earlier.

TEAE will be coded according to the latest Medical Dictionary for Regulatory Activities (MedDRA) terms and summarized by MedDRA System Organ Class (SOC) and Preferred Term.

Adverse Events of Special Interest (AESI) will be defined as following AEs:

- Adrenal hormone precursor accumulation-related AEs
- Hypocortisolism-related AEs
- Pituitary tumour enlargement-related AEs
- Arrhythmogenic potential and QT prolongation AEs

All AEs will be assessed according to incidence, grade, causality, outcome, action taken and seriousness. The details are provided in the safety analysis section 5.10.1 below.

5.3.4 Exploratory endpoint analysis

For late night salivary cortisol observed values at baseline and changes from baseline to Week 4, 8,12, 18, 24, 36 and to every 12 weeks until the earlier of loss to follow-up, death, or the end of the retrospective follow-up period or treatment discontinuation, descriptive summaries will be provided for every visit at which the cortisol markers are collected. Where applicable, proportion of participants with normal and/abnormal late night salivary cortisol will also be provided at every visit.

A participant level listing will be provided with all required details as per the eCRF.

5.3.5 Sensitivity Analysis

No formal sensitivity analysis will be performed, although the primary endpoint analysis will be performed on the mITT and On-Treatment populations as well.

5.3.6 Stratified Analysis

For the potential confounding identification objective, participants will be stratified if they received or did not receive other therapies for Cushing's syndrome (regardless of the type of therapy) from start of study treatment to week 12. The statistical null hypothesis states that the response rates at the end of the 12-week period (i.e., at Week 12) are the same between the participants with/without non-study CS treatment. To test this hypothesis, a Cochran-Mantel-Haenszel (CMH) exact test by non-study CS treatment (yes/no) will be performed using the ITT.

If the 2-sided p-value is $\leqslant$ 0.05, and the odds ratio (non-study CS medication treatment yes vs. no) is > 1, the null hypothesis will be rejected and the response rate at week 12 in the non-study CS treatment yes group will be considered higher than that in the non-study CS medication treatment no group.

5.4 Study Subjects

A clear accounting of the disposition of all participants with number and percentages of participants for whom No Objection Letter is obtained (Yes/No), Participants having NOL waiver (including deceased participants)-Yes/No, participants not meeting inclusion and exclusion criteria with primary reason for screen failure, participants meeting inclusion/exclusion criteria and participants receiving at least one dose of osilodrostat, and participants who discontinued prematurely (including death) by reason will be provided.

A listing of the participant disposition with the above details will be provided as per the eCRF.

5.5 Protocol Deviations

Major protocol deviations are defined as those deviations from the protocol that are likely to have an impact on the participant's rights, safety, well-being, and/or on the validity of the data for analysis.

The number of participants with protocol deviations will be summarized by category (Major or Minor) and deviation classification. Protocol deviations will be listed with date and study day of occurrence, deviation category, deviation description and analysis populations from which participant is excluded.

5.6 Demographic and Other Baseline Characteristics

A summary of demographic and baseline characteristics will be provided including Age (years), Gender, Height (cm), Weight (kg), BMI (kg / m^2).

A summary of clinical (disease) characteristics will include putative causation (i.e., adrenal adenoma, adrenocortical carcinoma, ectopic adrenocorticotropic hormone secretion, adrenal hyperplasia) and date of Cushing's syndrome diagnosis.

Descriptive summary statistics (n, mean (SD), median, minimum, maximum) or number and percentages will be provided for participants as applicable for the above-mentioned demographic components.

A participant level listing will be provided with all details of demographic components as per the eCRF.

5.7 Medical and procedural/surgical history

Medical and surgical history will be presented in a descriptive manner including number and percentages of past or current significant medical and surgical conditions.

A participant level listing of significant medical and surgical history will be provided with details of past or current significant medical or surgical history as per the eCRF.

5.8 Prior and Concomitant Medications

The prior and concomitant systemic therapy, radiotherapy and surgical therapy will be summarized in similar manner as described.

Medication start and stop dates will be compared to the date of first dose of osilodrostat to allow medications to be classified as either Prior only, both Prior and Concomitant, or Concomitant only. Medications starting after the completion/withdrawal date will be listed but will not be classified or summarized.

Medications that start and stop prior to the date of first dose of osilodrostat will be classified as Prior only. If a medication starts before the date of first dose of osilodrostat and stops on or after the date of first dose of osilodrostat, then the medication will be classified as both Prior and Concomitant. Medications will be classified as Concomitant only if they have a start date on or after the date of first dose of osilodrostat.

If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of first dose of osilodrostat (see section 5.11.2). Medications will be assumed to be Concomitant only, unless there is clear evidence (through comparison of partial dates) to suggest that the medication started prior to the first dose of osilodrostat. If there is clear evidence, such as an ongoing medical history with the same indication, to suggest that the medication started prior to first dose of osilodrostat and with no stop date, the medication will be assumed to be both Prior and Concomitant. If there is clear evidence to suggest that the medication stopped prior to first dose of osilodrostat, the medication will be assumed to be Prior only.

5.9 Safety Analysis

5.9.1 Adverse Events

All AEs, whether they are serious/non-serious, related/unrelated, and all “special situations” reported in participants’ charts within the data collection period should be collected. All AEs will be assessed according to incidence, grade, causality, outcome, action taken and seriousness.

TEAE and AESI were defined in section 5.3.3.5

An overview of adverse events will summarize the percentage of participants experiencing deaths, SAEs, AE reported as reason for discontinuation, TEAEs, and AEs possibly related to study drug.

The frequency and percentage of participants with following will be summarized using MedDRA preferred Term nested within SOC.

- TEAE
- TEAE by maximum severity
- TEAEs related to osilodrostat
- TEAE leading to osilodrostat dose interruption/adjustment
- TEAEs leading to study discontinuation
- SAEs including death
- SAEs by maximum severity
- SAEs related to osilodrostat
- Deaths
- AE of Special Interests (AESIs)

Adverse event summaries will be ordered in terms of decreasing frequency for SOC, and PT within SOC. For incidence counts, each participant will be counted only once within each Preferred Term and within each SOC. Percentages will be based on the number of participants in safety population. For events that are gender-specific, the denominator and computation of the percentage will include only participants from the given gender.

By-participant listings of all adverse events (including non-treatment-emergent events) recorded on the CRF, all TEATs, TEAEs leading to study discontinuation, SAEs including death, and deaths during the treatment period will be presented by participant, visit, preferred term, severity, and relationship to the study drug.

5.9.2 Deaths

A summary of all deaths and cause of death will be tabulated. The primary cause of death collected on the AE CRF page will be reported. If the primary cause of death is AE, the number of participants who have related AE and unrelated AE will be further reported.

A listing of all deaths will be provided.

5.9.3 Clinical Laboratory Evaluation

For analysing laboratory results, data from all sources (local laboratories) will be combined. The summaries will include all laboratory assessment. All laboratory assessments will be listed. Results will be reported for each visit at which collected through the last study visit.

Eligible laboratory data will be classified into grades according to NCI CTCAE v5.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be considered.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, The following summaries will be produced for the laboratory data (by laboratory parameter):

For laboratory tests where grades are defined by CTCAE

- Number and percentage of participants with worst post-baseline CTCAE grade (regardless of the baseline status). Each participant will be counted only for the worst grade observed post-baseline
- Number and percentage of participants meeting categorical liver function test criteria, including Hy's Law criteria for liver injury (ALT or AST > 3 x ULN and TBIL ≥ 2 x ULN and ALP < 2 x ULN). Each participant will be counted only for the worst grade observed post-baseline
- Shift tables from baseline to the worst post-baseline value and from baseline to the last post-baseline values using CTCAE grades will be produced for haematology, biochemistry, and urine laboratory parameters with CTCAE grades.

For laboratory tests where grades are not defined by CTCAE

- Shift tables from baseline to the worst post-baseline value and from baseline to the last post-baseline values will be produced using the low/normal/high classifications based on laboratory reference ranges.

Scheduled visit, and unscheduled visits will be included in above analysis.

Selected laboratory data will also be displayed by presenting summary statistics of change from baseline value.

The following listings will be produced for the laboratory data:

- Listing of all laboratory data with values flagged to show the corresponding CTCAE grades the classifications relative to the laboratory reference ranges
- Listing of notable laboratory abnormalities (i.e. CTCAE grade 3 or 4 laboratory toxicities).

5.9.4 Vital Signs, Physical Findings and Other Observations Related to Safety

Vital Signs

Vital signs of participants will be summarized include blood pressure (systolic and diastolic), weight, and BMI. Vital signs will be summarized for baseline, all post-baseline visits, and change from baseline to post-baseline visits. Descriptive statistics i.e., number (n), mean (SD), minimum (Min), median, maximum (Max), first and third quartiles and 95% CIs for means/medians, will be provided for systolic, diastolic blood pressure (mmHg) weight (kg), and BMI (kg/m^2).

The percentages of participants with treatment-emergent high or low vital signs at any time during the treatment period will be summarized. A treatment-emergent high results is defined as a change from a value less than the high limit at all baseline visits to a value greater than or equal to the high limit at any time during the treatment period. A treatment emergent low result is defined as a change from a value greater than the low limit at all baseline visits to a value less than or equal to the low limit at any time during the treatment period. For each vital sign, only participants who were normal (i.e., less than the high limit for treatment-emergent high, or greater than the low limit for treatment-emergent low) at all baseline visits and who have at least one non-missing post-baseline result will be included in the denominator when computing the percentages of participants with treatment -emergent high or low results. Table 2 will be used to define the low and high limits.

A participant level listing will be provided for vital signs with all required details as per the eCRF.

Table 2 Selected Categorical Limits for Blood Pressure, and Weight

Parameter	Low	High
Systolic BP (mm Hg) (supine or sitting – forearm at heart level)	≤90 and decrease from baseline ≥20	≥140 and increase from baseline ≥20
Diastolic BP (mm Hg) (supine or sitting – forearm at heart level)	≤50 and decrease from baseline ≥10	≥90 and increase from baseline ≥10
Weight (kg) (consistent clothing and timing in relationship to meals and voiding)	(Loss) decrease from baseline ≥ 7%	(Gain) increase from baseline ≥ 7%

ECG

Fridericia's formula (QTcF) will be used to calculate the heart rate-corrected QT interval (msec) based on the heart rate (HR bpm) and QT (msec) for centrally read data. These calculated QTc values will be used in ECG summary tables and listings. The formula is as follows:
$QTcF \text{ (in msec)} = QT/(RR)^{1/3}$

Results for each ECG parameter will be summarized at each visit for observed data and for changes from baseline.

The overall ECG assessment as determined by the investigator will be reported as “Clinical Significant – Yes”, or “Clinical Significant – No” and summarized by visit and across visits. A shift table of overall ECG assessment from baseline to the most extreme post-baseline value will be presented.

Additionally, the highest post-baseline value for QTc interval (using Fridericia’s correction) will be summarized descriptively as a categorical variable. Each QTcF value for a given subject will be grouped into 3 categories:

- QTcF interval ≥ 450 - < 480 msec
- QTcF interval ≥ 480 - < 500 msec
- QTcF interval ≥ 500 msec

The largest post-baseline change in QTcF measures will also be analysed as categorical variables. The change in QTcF in as given subject will be grouped into 2 categories:

- QTcF interval increases from baseline ≥ 30 msec
- QTcF interval increases from baseline ≥ 60 msec

Relevant ECG data will also be displayed in separate listings for:

- Subjects who shifted from normal or abnormal not clinically significant at baseline to abnormal clinically significant during the treatment period
- Subjects who had an abnormal clinically significant assessment at any time during the study
- Subjects who ever had a QTcF interval increase from baseline ≥ 30 msec during the treatment period
- Subjects who ever had any value of QTcF interval ≥ 450 msec at any visit

CS-Specific Physical examination

The results of physical examination of participants will be summarized descriptively at for baseline, all post-baseline visits with number and percentages of physical examination performed (yes/no), any abnormal findings (yes/no), and body systems as per the eCRF.

A participant level listing will be provided for physical examination with all required details as per the eCRF.

5.9.5 Extent of Exposure

The details of treatment exposure with osilodrostat will be summarized descriptively with number and percentages of dose up- and/or down-titration regimens, and reasons for titration, and duration of treatment.

If patients did not have temporary discontinuation, the duration of exposure will be
Duration of exposure (weeks) = (min (date of last date of study treatment, date of early termination, date of death) – date of first dose date of treatment + 1)/7

If patients had temporary discontinuation, the duration of exposure will be assessed specially case by case, the outcome of the case-by-case assessment will be documented in the Analysis Dataset Model (ADaM) related documents.

A summary of duration of exposure to study treatment will include categorical summaries and continuous summaries using appropriate unit of time.

A participant level listing will be provided for treatment exposure with all required details collected as per the eCRF.

Due to the high rate of missing end of treatment dates, the summary of exposure tables will be conducted by using two below approach A and B for the imputation of last date of exposure.

A. If end of study reason was due to adverse event, death, osilodrostat permanently discontinued, administrative reasons, end of retrospective follow-up period and last recorded dose did not change to 0mg prior to the end of study, the end of study date will be considered as the last date of exposure i.e., the end of treatment date. If last recorded dose changed to 0mg prior to the end of study, then the date when dose changed to 0mg will be considered as the last date of exposure. For other end of study reasons, the end of treatment date will be considered to be missing.
B. If treatment discontinuation date is not available and last recorded dose did not change to 0mg prior to the end of study, the end of study date will be considered as end of treatment date i.e., the last date of exposure. If last recorded dose changed to 0mg prior to the end of study, then the date when dose changed to 0mg will be considered as the last date of exposure.

5.10 **Subgroup Analysis**

i) Selected demographics and patient exposure by subgroups
   (1) Patient disposition
   (2) Summary of demographic and baseline disease characteristics
   (3) Concomitant medications
   (4) Summary of duration of exposure to Osilodrostat
   (5) Summary of dose change from initial dose by visits

ii) Selected efficacy endpoints by subgroups
   (1) Proportion of mUFC response by (week 4 to 60) mITT and On-treatment population
   (2) Change in mUFC from baseline by visits in mITT and On-treatment population
   (3) Proportion of salivary cortisol response by (week 4 to 60) mITT and On-treatment population
   (4) Proportion of composite measures of cortisol level response by (week 4 to 60) mITT and On-treatment population
   (5) Change in serum cortisol from baseline by visits in mITT and On-treatment population.

iii) Selected safety endpoints by subgroups
   (1) Overview of adverse events
   (2) Summary of adverse events of special interests by system organ class and preferred term

5.11 Handling of Missing and Uninterpretable Data

5.11.1 Missing data

Based on the nature of the study (observational, non-comparative, retrospective), missing data will not be replaced in the statistical analysis of primary and secondary endpoints.

If there is a significant number of missing values for a subject (or if there is confirmed data appearing spurious), a decision will be made following consultation with the sponsor regarding the handling of these data in summaries, prior to DB lock.

Only missing dates will be imputed where applicable and the imputation rule corresponding to missing date is given in section 5.10.2 below.

5.11.2 Missing or incomplete dates

In all listings, missing or incomplete dates should be left as they have been recorded. However, in determining treatment period and/or days since a certain time point, the following conservative approach will be used to impute the missing date values:

Medical History/Disease Diagnosis

- Missing/incomplete dates will be assumed to have occurred prior to any study treatment, unless there is evidence to prove otherwise
- Partial dates should be reviewed to ensure they did not occur following any study treatment.

AE/Concomitant Medication (Conmed)

- Day only missing
  a. If year/month of AE/Conmed equals year/month of the first dose date, then impute start day of the first dose date
  b. If year of AE/Conmed equals to the year of the first dose date and month of AE/Conmed is less than the month of the first dose date, then impute last day of the month
  c. If year of AE/Conmed equals to the year of the first dose date and month of AE/Conmed is greater than the month of the first dose date, then impute first day of the month
  d. If year of AE/Conmed is less than the year of the first dose, then impute last day of the month
  e. If year of AE/Conmed is greater than the year of the first dose, then impute first day of the month

- Month/Day only missing
  a. If year of AE/Conmed equals year of the first dose date, then impute start day and month of the first dose date
  b. If year of AE/Conmed is less than the year of the first dose date, then impute 31Dec
  c. If year of AE/Conmed is greater than the year of the first dose date, then impute 01Jan

- Start date is completely missing
  a. If the first dose date is greater than the AE/Conmed end date, then the AE/Conmed start date equals the AE/Conmed end date
  b. If the first dose date is less than the AE/Conmed end date, then the AE/Conmed start date equals the start date of first dose
  c. If the AE/Conmed end date is missing, then the AE/Conmed start date equals the start date for the first dose

- Imputed start date, where end date is not missing
  a. Check, if the imputed AE/Conmed start date is greater than the AE/Conmed end date, then the imputed start date should be updated to match the AE/Conmed end date

Osilodrostat Administration date

- Day only missing of first dose date
  a. Imputed missing day as 15 of the month.

- Day only missing
  a. Imputed missing day as 15 of the month, unless other dates related to the dose change are occurring before the 15, in that case the day should be the same of the event occurring in concomitance.

- Day and month missing
  a. If the dose change is related to an event (adverse event, study discontinuation, etc.) imputed missing month as the month of the event or the visit month, and impute missing day as 15 unless the other dates related to the dose change are occurring before the 15, in that case the day should be the same of the event occurring in concomitance.

5.11.3 Outliers

Any outlier identified prior to DB lock which is impossible/implausible could be excluded from the analysis. If any outliers are identified after DB lock, actions with the sponsor should be defined by data management.

5.12 Determination of Sample Size

There is no statistical hypothesis testing for this study; therefore, the sample size is not based on formal statistical considerations and, instead, is based on practical considerations.
Historical data will be collected from approximately 100 participants with a diagnosis of non-CD CS with an aetiology of adrenal adenoma, adrenocortical carcinoma, adrenal hyperplasia, or ectopic adrenocorticotropic hormone secretion treated with osilodrostat as follows:

a) Under the April 2019 French ATU (5th Apr 2019) or
b) Under conditions of routine clinical practice after commercialization of osilodrostat in France since June 2020.

5.13 CHANGES FROM PROTOCOL

Currently the SAP elaborates analyses as planned in the protocol and some related analysis in addition to protocol specified analysis. This section is kept for documenting any changes made to the planned analyses in the study protocol due to various circumstances for e.g., a protocol amendment. Any such changes (if occurs) will be documented, and this section of SAP will be updated with all necessary details related to the change.

6 REFERENCES

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