RECORDATI

Recordati Research and Development

LCI699 (osilodrostat)

Clinical Trial Protocol CLCI699C2X01B

An open-label, multi-center, roll-over study to assess long term safety in patients with endogenous Cushing's syndrome who have completed a prior Novartis-sponsored osilodrostat (LCI699) study and are judged by the investigator to benefit from continued treatment with osilodrostat

Document type:	Amended Protocol Version
EUDRACT number:	2017-002840-34
ClinicalTrials.gov Identifier:	NCT03606408
Version number:	02 (Clean)
Clinical Trial Phase:	II b
Release date:	06-May-2020
Sponsor:	RECORDATI AG - Lindenstrasse 8, 6340 Baar, Switzerland tel: + 41 (0) 61 205 61 00
CRO:	IQVIA

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List of abbreviations

ACE	Angiotensin-converting enzyme
ACTH	Adrenocorticotropic Hormone
AE	Adverse Event
ALT	Alanine Aminotransferase/Glutamic Pyruvic Transaminase (GPT)
ALP	Alkaline Phosphatase
AST	Aspartate Aminotransferase/Glutamic Oxaloacetic Transaminase (GOT)
b.i.d.	bis in die/twice a day
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CD	Cushing's Disease
CK	Creatine Kinase
CI	Confidence Interval
CS	Cushing's Syndrome
CMV	Cytomegalovirus
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical Study Report
CSR addendum	An addendum to Clinical study report (CSR) that captures all the additional information that is not included in the CSR
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DB	Database
DDI	Drug Drug Interaction
DILI	Drug-Induced Liver Injury
DLT	Dose Limiting Toxicity
CMO&PS	Chief Medical Office and Patient Safety
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
EOT	End Of Treatment
FAS	Full Analysis Set
FPFV	First Patient First Visit
GGT	Gamma-Glutamyl Transferase
HbA1c	Hemoglobin A1c
hCG	Human Chorionic Gonadotropin
HSV	Herpes Simplex Virus
IUD	Intrauterine Device
IUS	Intrauterine System
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
LFT	Liver Function Test
LLN	Lower Limit Normal
MRI	Magnetic Resonance Imaging

MoA	Mechanism of Action
mUFC	Mean Urinary Free Cortisol
NCI CTC	National Cancer Institute Common Terminology Criteria
PHI	Protected Health Information
PK	Pharmacokinetics)
PT	Prothrombin Time
REB	Research Ethics Board
SAE	Serious Adverse Event
s.c.	subcutaneous
SD	Standard Deviation
SMR	Standardized Mortality Ratio
SRS	Stereotactic radiosurgery
TBIL	Total Bilirubin
TdP	Torsades des Pointes
WOCBP	Women of childbearing potential
UFC	Urinary Free Cortisol
ULN	Upper Limit Normal

Amendment 02 (06-May-2020)

Amendment rationale

As of 8 April 2020, 100 patients are enrolled in this trial. Within the framework of a worldwide purchase agreement between Novartis and Recordati (an international pharmaceutical group with a specialized business dedicated to treatments for rare diseases) on July 2019, the two Companies agreed to a sponsorship transfer of this study with LCI699 (osilodrostat).

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 trial-related activities on behalf of Recordati.

An update on the investigational medicinal product is also included, since osilodrostat (Isturisa®) has been granted an approval from the European Commission on 9th January 2020 for the treatment of endogenous Cushing syndrome in adults, and from FDA on 6th March 2020 for adults with Cushing's disease who either cannot undergo pituitary gland surgery or have undergone the surgery but still have the disease.

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.
- Activities performed by the CRO IQVIA on behalf of Recordati has been mentioned.
- Section 1.1.4.2 (Clinical experience) was updated in line with EMA and FDA approval for use in the adult population.
- Section 6.1.1 (Investigational and control drugs): IQVIA vendor has been inserted as a new site for packaging, and as responsible for labelling and drug supply at sites after sponsorship transfer
- Section 13.3 (Publication of study protocol and results) mention to the Novartis publication policy has been deleted.

IRBs/IECs

A copy of this amended protocol version 02 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 01 (18-Mar-2019)

Amendment rationale

As of 29th Jan 2019, 23 patients are enrolled in this trial. This amendment was required due to the request of Health Authorities to specify the safety monitoring in the study. Therefore, the following safety assessments have been defined at scheduled study visits: physical examination, body weight and blood pressure, laboratory evaluations, ECG and pituitary MRI.

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 changes being made to the protocol due to this amendment are incorporated in the following sections:

- Cover page: Authors were removed
- Table of contents: The text was updated reflecting the changes in the amended protocol.
- List of abbreviations: The list of abbreviations was updated.
- Protocol Summary: the text for secondary objectives, safety assessment and data analysis was updated
- Table 2-1 : Secondary safety objective and secondary safety objective endpoint added
- Section 3-1: The word “reimbursed” was removed from the paragraph describing the duration of subject treatment.
- Section 4.1: The text describing the duration of the study and subject treatment was deleted as it is a duplicate from section 3.1.
- Section 4.2: Text was added as a guidance to the Investigator for dose modification.
- Section 4.5: Procedures added to the existing ones to mitigate the potential risks related to the administration of osilodrostat. The following text is also added “Drug administration record for dosing of osilodrostat will be completed at each visit”.
- Table 8-1 : Content is updated to reflect the additional safety assessments
- Section 8.4 : Text added specifying that safety assessments must be maintained in source documentation for each patient
- Section 8.4.1 : Physical examination is described
- Section 8.4.2 : Body weight and blood pressure procedures are described
- Section 8.4.3 : Laboratory evaluations are listed
- Section 8.4.4 : Text for ECG is added
- Section 8.4.5: Text is added specifying the frequencies of the pregnancy tests.
- Section 8.4.6 : The section is added to describe the MRI process and assessment
- Section 8.4.7 : This section was renumbered due to the insertion of sections 8.4.1, 8.4.2 and 8.4.6
- Section 9.1.1: Text was added for clarification. The word “reimbursed” was removed from the paragraph describing the circumstances for study treatment discontinuation.

- Section 12.5. The following paragraph was added “The secondary safety objective of the study is to evaluate long term safety, assessed using laboratory data, vital signs (blood pressure and body weight), ECG and pituitary MRI. Details of the specific analyses for each type of safety endpoint is given in Section 12.5.1.”
- Section 12.5.1 Analysis methods for additional safety assessments added.

Glossary of terms

Assessment	A procedure used to generate data required by the study
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained
Medication number	A unique identifier on the label of medication kits
Patient	An individual with the condition of interest for the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Subject	A trial participant (can be a healthy volunteer or a patient)
Study treatment	Any single drug or combination of drugs or intervention administered to the subject as part of the required study procedures.
Study treatment discontinuation	When the subject permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, etc.
Roll-over study	A roll-over study allows patients from previous parent studies for similar or different indications to continue treatment with the same drug after completion of the parent study.
Variable	A measured value or assessed response that is determined from specific assessments and used in data analysis to evaluate the drug being tested in the study

Protocol summary

Full Title	An open-label, multi-center, roll-over study to assess long term safety in patients with endogenous Cushing's syndrome who have completed a prior Novartis-sponsored osilodrostat (LCI699) study and are judged by the investigator to benefit from continued treatment with osilodrostat
Brief title	Roll-over study in patients with endogenous Cushing's syndrome
Sponsor and Clinical Phase	Recordati, IIb
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is the evaluation of long-term safety of osilodrostat in patients who have already received osilodrostat treatment in a previous Global Novartis-sponsored trial and who, based on investigators' judgement, will continue benefiting with its administration.
Primary Objective(s)	To evaluate the long term safety data with osilodrostat treatment i.e. adverse events (AEs) and serious adverse events (SAEs).
Secondary Objectives	To evaluate clinical benefit as assessed by the Investigator To evaluate the long term safety of osilodrostat treatment, as assessed by physical examination, laboratory data, vital signs, ECG and pituitary MRI.
Study design	This is a multi-center, open label study to evaluate the long term safety of osilodrostat in patients currently being treated in a Global Novartis-sponsored study and who are judged

	by their parent study Investigator as benefiting from the current study treatment. The study is expected to remain open for approximately 5 years (or until 31-Dec-2023 in the UK) from First Patient First Visit (FPFV). Patients will continue to be treated in this study until they are no longer benefiting from their osilodrostat treatment as judged by the Investigator or until one of the protocol defined discontinuation criteria is met.
Population	Patients with endogenous Cushing's syndrome who are currently enrolled in a Global Novartis-sponsored study and benefiting from treatment with osilodrostat, as determined by the Investigator.
Key Inclusion criteria	1. Patient is currently participating in a Global Novartis-sponsored study receiving osilodrostat for any type of endogenous CS and has fulfilled all the requirements in the parent study. 2. Patient is currently benefiting from treatment with osilodrostat, as determined by the Investigator. 3. Patient has demonstrated compliance, as assessed by the Investigator, with the parent study protocol requirements. 4. Patient is willing and able to comply with scheduled visits and treatment plans. 5. Written informed consent/adolescent assent obtained prior to enrolling into the roll-over study.
Key Exclusion criteria	1. Patient has been permanently discontinued from osilodrostat study treatment in a parent Novartis-sponsor study. 2. Patients who are receiving osilodrostat in combination with unapproved or experimental treatments for any type of endogenous CS. 3. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory evaluation.
Study treatment	Osilodrostat, film-coated tablets up to 30 mg b.i.d, oral use
Efficacy assessments	At every quarterly visit, the Investigator is required to confirm that the patient continues to have clinical benefit and may continue receiving study treatment.
Safety assessments	AEs/SAEs, physical examination, body weight and blood pressure, blood chemistry tests, hematology, hormones, ECG and pituitary MRI.
Data analysis	The assessment of safety will be based mainly on the frequency and severity of AEs/SAEs and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data, such as physical examination, vital signs (blood pressure and body weight), ECG and Pituitary MRI or CT will also be presented. Proportions of patients with clinical benefit as assessed by the Investigator will be summarized at scheduled visits.
Key words	Osilodrostat, endogenous Cushing's syndrome, roll over study, long term safety

IRBs/IECs

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

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

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

1 Introduction

1.1 Background

1.1.1 Epidemiology and pathogenesis of Cushing's syndrome

Cushing's syndrome (CS) is a rare disorder with a reported incidence of 0.7–2.4 per million population per year. In European countries and in the US, the prevalence rates have been reported to range from 19 to 79 cases per million inhabitants, with the highest prevalence (79 cases per million) reported from New Zealand. In a survey conducted in Japan by the Ministry of Health, Labour and Welfare in 1997, the prevalence of CS has been reported to be approximately 1250 cases.

CS is characterized by a chronic excess of cortisol secretion, which results in numerous clinical features that are associated with a higher mortality compared with the general population, if not appropriately treated (Pivonello et al, 2008).

CS can be either exogenous or endogenous. The most common cause of exogenous CS is iatrogenic due to the external administration of excessive doses of glucocorticoids.

Endogenous CS is classified as either adrenocorticotropic hormone (ACTH)-dependent or ACTH-independent. ACTH-dependent CS accounts for 80%–85% of cases. Of these, 75%–80% are due to ACTH production from a pituitary adenoma (Cushing's disease [CD]), 15%–20% are due to ACTH production from non-pituitary tumors (ectopic ACTH syndrome) and <1% are caused by corticotrophin-releasing hormone (CRH)-producing tumors.

ACTH-independent CS accounts for 15%–20% of endogenous CS in adults; 90% are unilateral adrenal tumors. Of these, adenomas are the cause in ~80% of the cases, while the others are adrenocortical carcinoma.

Cushing's disease (CD) is the most common cause of CS (70% of cases) in Western countries, while it makes up a smaller proportion of the CS population in Japan (35.8%). It is caused by excessive secretion of cortisol from the adrenal glands as a consequence of excessive ACTH secretion from a pituitary tumor, generally an adenoma (90%), whereas a carcinoma is a very rare cause of the disease (less than 10%). It affects adults aged 20-50 years-old more commonly with a marked female preponderance (Pivonello et al 2008; Newell-Price et al 2006).

Endogenous CS is characterized by chronic hypercortisolism, which results in a variety of metabolic abnormalities and co-morbidities that collectively lead to an overall 4-fold higher mortality rate than age- and gender-matched subjects in the general population (Arnaldi et al, 2003).

The clinical manifestations are variable and include obesity affecting mainly the face, neck, trunk, and abdomen, thinned skin, purple striae, muscular weakness, fatigue, hypertension, diabetes mellitus (DM), neuropsychiatric disorders, acne, hirsutism, and menstrual irregularities (Arnaldi et al, 2012).

There is an increased cardiovascular risk and it is mainly due to the metabolic syndrome, insulin resistance, weight gain, glucose intolerance, dyslipidemia and hypercoagulation.

Normalization of hypercortisolism is expected to improve or reverse the increased morbidity and mortality associated with the untreated disease. Published data have suggested that recovery from the co-morbidities does occur, but may be delayed or incomplete (Valassi, et al 2012; Arnaldi, et al 2012). The duration and severity of chronic hypercortisolism may impact the reversibility of the co-morbidities associated with CD (Feelders, et al 2012).

However, mortality studies have consistently shown that the mortality rate is significantly impacted by the biochemical status of the disease, i.e., persistent/recurrent hypercortisolism compared to biochemical remission of the disease.

A meta-analysis of published mortality studies (Clayton, et al 2011) showed that the standardized mortality ratio (SMR) is much higher in CD patients with persistent hypercortisolism (SMR=5.5) than those in remission (SMR=1.2).

1.1.2 Current treatment modalities

Surgical resection of the source of glucocorticoid excess (pituitary adenoma, non-pituitary tumor-secreting ACTH or adrenal tumor[s]) remains the first-line treatment of all forms of endogenous CS.

The first line-treatment of CD is mainly represented by the surgical removal of the pituitary tumor by TSS (Pivonello 2015). Post-surgical remission rates of 70-80% have been reported. However, a 25% incidence of recurrent hypercortisolism has been reported at 10 years of follow-up (Bochicchio et al 1995; Sonino et al 1996). With a second pituitary surgery (re-operation), success rates are lower and complications are higher than with primary pituitary surgery; therefore patients should be carefully selected (Fleseriu, et al 2007; Friedman, et al 1989).

In the International Consensus Statement on the treatment of ACTH-dependent CS (Biller, et al 2008), the goals of treatment are stated as: reversal of clinical features; normalization of biochemical changes with minimum morbidity; and long-term control without recurrence.

Medical therapy is an attractive option for patients with CD who have persistent or recurrent hypercortisolism after primary pituitary surgery with or without radiation, and patients with *de novo* CD who are not surgical candidates for medical reasons, refuse to undergo surgery, or do not have access to a specialized center with experience in pituitary surgery.

Pasireotide (Signifor®), a second generation somatostatin analogue, is currently approved in the US and in EU, and many other countries, for the treatment of CD.

Mifepristone, a glucocorticoid receptor antagonist, is approved in the US for the treatment of hyperglycemia secondary to hypercortisolism in adult patients with endogenous CS who have type 2 diabetes mellitus or glucose intolerance.

Several other drugs have been used with and without regulatory approval for the treatment of CD, including the steroidogenesis inhibitors ketoconazole and metyrapone (both approved in Europe), mitotane (adrenolytic agent), and cabergoline (dopamine agonist).

Pituitary irradiation is an option for patients who are not surgical candidates or have persistent or recurrent hypercortisolism following primary pituitary surgery. However, the response to pituitary irradiation is slow and is related to the type of radiation administered. The two most

commonly used radiation modalities are stereotactic radiosurgery (SRS), which consists of a single high-dose treatment (e.g. proton beam, gamma knife or cyber knife), and conventional, fractionated radiation (linear accelerator). SRS is not only more convenient to the patient; it also has a faster onset of biochemical remission median of 17 months (Sheehan, et al 2013), than with conventional fractionated radiation, with an onset of 2-3 years (Loeffler and Shih, 2011). In some cases of conventional fractionated radiation, remission may be delayed until 10 years or longer (Losa, et al 2010; Minniti, et al 2007). The long term complications include hypopituitarism (Newell-Price, et al 2006), secondary malignant tumors (Sedney, et al 2012), and possibly an increased risk of death from cerebrovascular disease post-radiation (Ayuk 2012).

Bilateral adrenalectomy in ACTH-dependent CS may be used when surgery and medical therapy are unsuccessful, or based on patient preference. It leads to rapid resolution of hypercortisolemia and related morbidity. However, after bilateral adrenalectomy, patients need lifelong glucocorticoid and mineralocorticoid replacement.

Another concern with bilateral adrenalectomy in patients with CD is the development of Nelson's syndrome (local tumor growth with mass effects and increased ACTH levels causing hyperpigmentation

1.1.3 Unmet medical need

The treatment of patients with CS still represents a challenge, especially for patients with CD since the available treatments do not lead to biochemical control in quite a large number of patients and many of them lose biochemical control over time.

Therefore, there is an unmet medical need to develop new drugs with improved safety, efficacy and a more patient-friendly profile.

Osilodrostat, a novel adrenal-directed steroidogenic inhibitor, is under evaluation, due to its safety and efficacy profile, as demonstrated by preliminary data from the LINC 2 study, conducted in patients with Cushing's disease.

Based on these results osilodrostat shows promise in fulfilling an unmet medical need in all types of endogenous CS.

1.2 Purpose

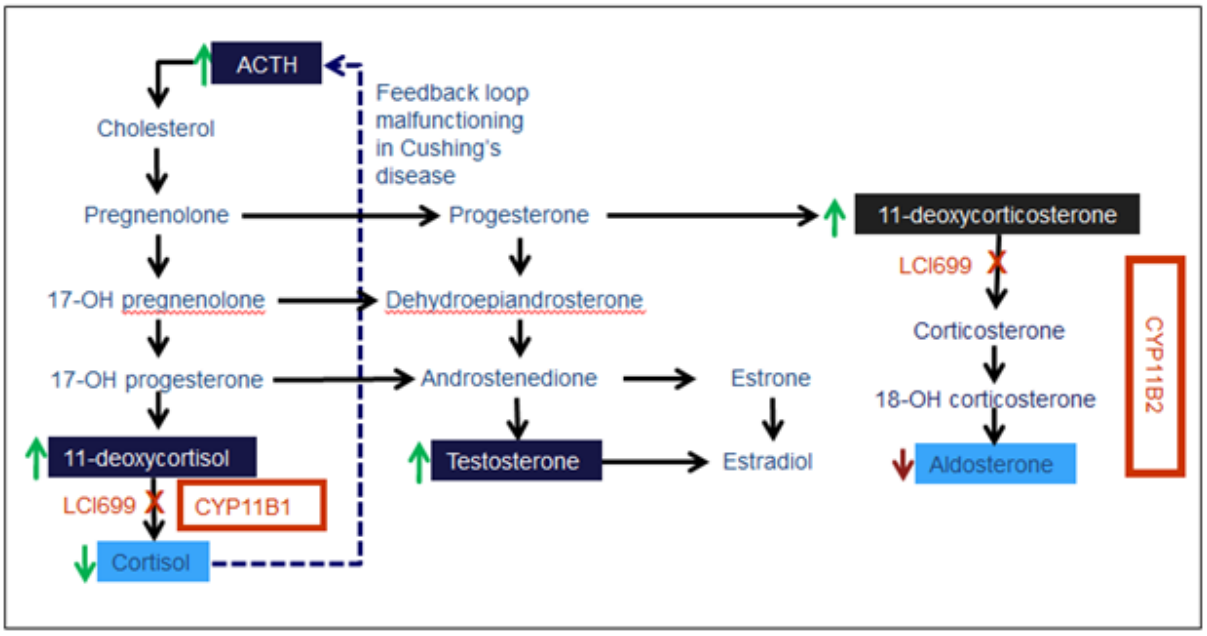
1.2.1 Overview of osilodrostat

Osilodrostat (company research code: LCI699) is a potent, oral inhibitor of 11β-hydroxylase (CYP11B1), the enzyme that catalyzes the last step in the biosynthesis of cortisol. This provides the rationale for investigating the use of osilodrostat in endogenous causes of CS.

It is manufactured as a phosphate salt and available in film-coated tablets of 1 mg, 5 mg and 10 mg.

The mechanism of action of osilodrostat is depicted in Figure 1-1 below.

Figure 1-1 Mechanism of action of osilodrostat in Cushing's Syndrome



1.2.1.1 Non-clinical experience

For detailed non-clinical pharmacokinetics and toxicity findings, please refer to the [Investigator Brochure].

1.2.1.2 Clinical experience

Currently, osilodrostat (Isturisa®) has been granted an approval:

- from the European Commission on 9th January 2020 for the treatment of endogenous Cushing syndrome in adults and
- from FDA on 6th March 2020 for adults with Cushing's disease who either cannot undergo pituitary gland surgery or have undergone the surgery but still have the disease.

1.2.1.2.1 Results of study LCI699C2201

Results of LCI699C2201 study in CD.

The purpose of the LCI699C2201 study was to determine whether the ability of osilodrostat to inhibit 11β-hydroxylase could safely reduce UFC (Urinary Free Cortisol) in patients with CD.

This was initially studied over a 10-week treatment duration Proof-of Concept (Part I). Part II of the study aimed to further evaluate the observations from the Part I by enrolling a cohort of patients who participated in Part I and a new cohort (Expansion cohort) of patients and evaluating the long-term efficacy and safety of osilodrostat treatment.

In Part I, osilodrostat was effective in controlling cortisol production in all 12 patients studied. At daily osilodrostat doses between 2 mg twice a day (b.i.d.) and 50 mg b.i.d., 24-hour cortisol decreased rapidly and normalized at least once in all patients studied. In general at 5 mg b.i.d.

patients showed cortisol reduction after 2 weeks (at first cortisol measurement after dose titration).

The primary endpoint, defined as cortisol ≤ Upper Limit Normal (ULN) or ≥ 50% decrease from baseline at Day 70, was achieved by all patients. Overall, the mean time to response (UFC normalization or ≥ 50% reduction from baseline) was 34.3±14.1 days. The mean daily dose [± Standard Deviation (SD)] of osilodrostat required to reach the primary endpoint was 13.5±13.9 mg b.i.d. with 75% of patients normalizing cortisol on ≤ 10 mg b.i.d. At Day 84, two weeks after osilodrostat was withdrawn, cortisol levels increased to a mean of 4-fold above upper limit of normal (ULN).

Significant decreases in mean plasma cortisol and aldosterone from baseline (-60% and -70%, respectively) and marked increases in their precursors from baseline (11-deoxycortisol [13-fold] and 11-deoxycorticosterone [42-fold], respectively) and ACTH [2.4-fold] were observed at Day 70. These biochemical changes were as expected based on the mechanism of action of the drug, i.e., primarily related to hypocortisolism, hypoaldosteronism, accumulation of their precursors, and increase in ACTH from baseline.

In Part II, 17 out of 19 patients completed 22 weeks of treatment and 15 had normal cortisol levels at week 22 (79%). During treatment with osilodrostat, the mean cortisol levels decreased quickly and stabilized to a normal level (11 to 138 nmol/24h) at Week 4. After Week 4, normal mean cortisol levels were observed through the study up to Week 22. All patients attained UFC normalization at least once during the study, and no patient "escaped" UFC control. The study is ongoing.

- Two phase III multi-center studies are ongoing:
  a. C2301: this is a double-blind, randomized, withdrawal study following a 24 week, single-arm, open-label, dose titration and treatment period to evaluate the safety and efficacy of osilodrostat in the treatment of patients with CD. Primary endpoint: proportion of randomized patients in each treatment group with mUFC ≤ ULN at week 34 who neither discontinued nor had dose increase above the week 24. This study has enrolled 137 subjects with CD.
  b. C2302: this is a randomized, double-blind, placebo-controlled 48-week study with an initial 12 week placebo-controlled period to evaluate the safety and efficacy of osilodrostat in patients with CD. Primary endpoint: proportion of randomized patients with a complete response at Week 12. The study plans to enroll 69 subjects with CD.
- One phase II multi-center study is ongoing in Japan:
  a. C1201: this is an open label, dose titration, multi-center study to assess the safety, tolerability and efficacy of osilodrostat in patients with all types of endogenous CS, except CD.

1.2.1.2.2 Overview of safety

In the clinical trials for the treatment of hypertension or primary hyperaldosteronism, osilodrostat was tolerated with the overall incidence of adverse events being similar to placebo.

Adverse events (AEs) were generally of mild to moderate intensity. Both Serious Adverse Events (SAEs) and discontinuations due to AE were infrequent, and were reported at a rate

similar to placebo in the hypertension studies. The most common AEs across these studies were: headache, dizziness (including postural dizziness), nausea, diarrhea and fatigue. There were also AEs of hyperkalemia and impaired ACTH-stimulated cortisol response in these trials, which are consistent with the potential for hypocortisolism and hypoaldosteronism.

Overall, in patients with CD (study CLCI699C2201), safety data from the 10-week analysis has also showed that osilodrostat was well tolerated with similar common AEs to those in the hypertension trials, including: fatigue, nausea, vomiting, diarrhea, headache, dizziness, hypokalemia and muscle spasms.

In Part I of the study, all 12 patients (100%) experienced adverse events but these were generally grade 1 or grade 2 (National Cancer Institute Common Terminology Criteria (NCI CTC)). Fatigue, muscle cramps, dizziness and gastrointestinal events were the most common events suspected to be drug related. Four patients reported AEs consistent with cortisol and/or aldosterone withdrawal; dose reductions or temporary dose interruption in these patients improved the symptoms. There were no discontinuations related to study drug and no serious adverse events of suspected drug relationship.

In Part I, SAEs of decreased hemoglobin, tachycardia, chest pain and reactivation of Takayasu's arteritis were reported in one patient. The events were attributed to progression of the preexisting conditions and were not suspected to be related to study drug.

In Part II, osilodrostat was also generally well tolerated throughout the study. Of the 19 enrolled patients, 17 patients completed the 22 weeks treatment period with a median duration of exposure of 25.1 and 38.9 weeks in the Expansion cohort and Follow-up cohort, respectively. The safety findings identified in the interim analysis (data cut-off date: 23-Dec-2013) that was performed after the last patient had completed 22 weeks of treatment showed that except for one patient in the Expansion cohort, all patients experienced AEs, grade 1 and grade 2 in most of the cases. Adrenal insufficiency, nausea, fatigue and increase levels of oxycorticosteroids, blood corticotrophin, and blood testosterone were the most common AEs suspected to be drug related [by Preferred Term]. There were no new safety concerns during the Extension Period to Month 31. This study is ongoing.

In Part II (31-month analysis), a total of 9 SAEs were reported in 4 patients, including (by preferred term) pituitary-dependent Cushing's syndrome (in 2 patients), electrocardiogram QT prolonged, food poisoning, gastroenteritis, headache, non-cardiac chest pain, pituitary tumor and pituitary tumor benign.

Of these, one event of QT prolongation was reported as related to study drug by the Investigator, however the event developed in the context of gastroenteritis with anorexia and dehydration. There were no reported cardiac symptoms or cardiac arrhythmia. QT prolongation resolved after osilodrostat was discontinued, and did not reoccur when osilodrostat was re-started at a lower dose.

Other notable events included pituitary tumor enlargement and pituitary tumor reported in two patients. Both patients had elevated ACTH level. The study treatment was stopped in both patients because of pituitary surgery. The Investigators did not suspect a relationship between the events and treatment with osilodrostat.

In reviewing the clinical trial experience with osilodrostat to date, AEs have been identified that are consistent with the mechanism of action of the drug as an inhibitor of both cortisol and aldosterone synthesis. These can be summarized as follows:

- Changes in adrenal hormones: cortisol decreased, aldosterone decreased, and their precursors (11-deoxycortisol, 11-deoxycorticosterone) increased
- Change in pituitary hormone: ACTH increased
- Changes in electrolytes: potassium increased or decreased
- Changes in body weight and blood pressure: potentially increased by mineralocorticoid effect of the aldosterone precursor 11-deoxycorticosterone
- Changes in sex hormones: testosterone and estradiol increased (testosterone more than estradiol)

In addition, treatment with osilodrostat can potentially result in neutropenia, which is considered to be an indirect effect of cortisol reduction, as reported in the literature. During hormonal control, a significant decrease of neutrophil count, which is commonly elevated in patients with CD, has been reported demonstrating the effect of glucocorticoids on these blood cells (Masri-Iraqi et al 2014). This effect has also been observed with osilodrostat in the CD trials and has included cases of neutropenia which were associated with cortisol levels that were either below normal or have had a rapid and substantial decline from baseline. In the cases observed to date, neutropenia has rapidly reversed with discontinuation of osilodrostat, and has also reversed when osilodrostat was continued, typically with decreasing doses.

For a comprehensive review of clinical safety data with osilodrostat, see the [Investigator's Brochure].

1.2.1.2.3 Osilodrostat: QT/QTc in healthy volunteers

The potential impact of osilodrostat on cardiac repolarization potential was assessed in the definitive ICH E14 compliant thorough QT Study (TQT) study LCI699C2105 in 86 healthy male and female subjects.

Based on the predicted exposure levels, the predicted maximum mean QTcF on osilodrostat 30 mg is 6.3 ms (CI 5.13, 7.42).

The results remained below the QTcF effect of regulatory concern (i.e., an upper boundary of the 90% CI < 10 ms) and fully support the use of LCI699 doses up to 30 mg b.i.d.

2 Objectives and endpoints

Objectives and related endpoints are described in Table 2-1 below.

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s) ● To evaluate long term safety data	**Endpoint(s) for primary objective(s)** ● Frequency and severity of AEs/SAEs;
Secondary Objective(s) ● To evaluate clinical benefit as assessed	**Endpoint(s) for secondary objective(s)** ● Proportion of patients with clinical benefit as assessed by the Investigator at scheduled visits

Objective(s)	Endpoint(s)
by the investigator. ● To evaluate long term safety data	● Frequency, severity and summaries of relevant safety assessments. Safety assessments include: laboratory evaluations, vital signs (blood pressure and body weight), ECG and pituitary MRI.

3 Study design

3.1 Description of study design

This is a multi-center, open label phase IIb study to evaluate the long-term safety of osilodrostat in subjects receiving osilodrostat in a Global Novartis-sponsored study which has fulfilled its requirements for the primary objective, and who are judged by their parent study Investigator as benefiting from continued treatment with osilodrostat.

There will be no screening period for this study. Eligible subjects can start their treatment with osilodrostat as soon as they are enrolled in the study. The first study visit will be scheduled at the time of the last study visit for the parent study. At that time, sufficient supply of osilodrostat to cover a period of approximately 3 months may be dispensed to the subject/caregiver or as per local practice.

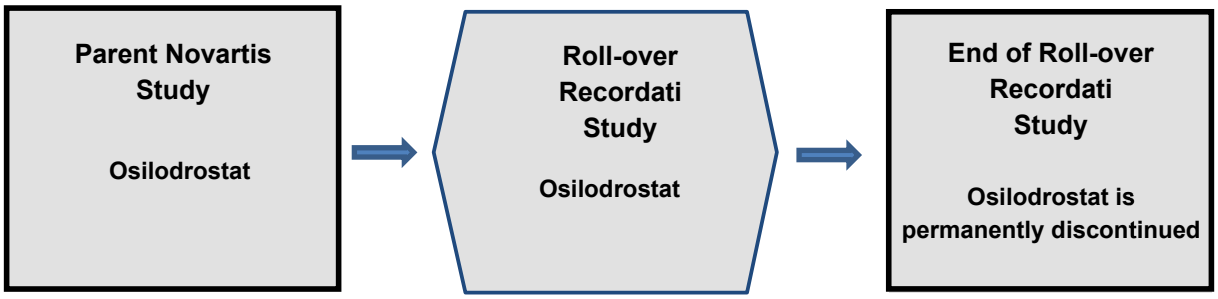
Subjects must return to the study center at least on a quarterly basis (every 12 weeks ± 2 weeks) for safety and clinical benefit assessments, and resupply of study medication. Drug dispensing and administration information and adverse events will be collected. The subject may return to the clinic at any given time as per standard of care or treating physician recommendation; however, only the quarterly study visits will be recorded in the Case Report Form (CRF). Study medication dispensed will be recorded in the CRF dose administration page.

All adverse events and serious adverse events, including pregnancy, will be collected throughout the study.

The study is expected to remain open for approximately 5 years (or until 31-December-2023 in the UK) from First Patient First Visit (FPFV). Subjects will continue to be treated in this roll-over study until they are no longer benefiting from their osilodrostat treatment as judged by the Investigator or until osilodrostat is commercially available or until one of other discontinuation criteria is met (please refer to Section 9.1.1). At every quarterly visit (every 12 weeks ± 2 weeks), the Investigator is required to confirm that the subject continues to have clinical benefit and may continue receiving study treatment.

A subject will reach the end of study when osilodrostat treatment is permanently discontinued.

Figure 3-1 Study Design



4 Rationale

The purpose of this study is to evaluate the long-term safety of osilodrostat and to allow its continued supply to subjects who are currently receiving osilodrostat treatment in a Global Novartis- sponsored study that has reached its study objectives.

These subjects are judged by the parent study Investigator as benefiting from continued treatment with osilodrostat and by the fact that, they would not be able to access osilodrostat outside a clinical trial.

4.1 Rationale for study design

This is a multi-center, open-label, phase IIb roll-over study to evaluate the long-term safety of osilodrostat in subjects who have completed the parent studies and are judged by the parent study Investigator as benefiting from treatment.

This roll-over study will not include a screening phase, at the completion of the parent study, as subjects will directly transfer from the parent studies. When their participation in the parent study has finished, eligible patients will start receiving osilodrostat only after they have signed the Informed Consent and have met the selection criteria for this roll-over study.

4.2 Rationale for dose/regimen and duration of treatment

At the time of transition to this roll-over study, the starting dose should be the same as the last dose that was given at the last visit in the parent study. During the roll-over study, dose modification may be done at the discretion of the Investigator following the guidelines in Section 6.5.

The maximum dose may not exceed 30 mg bid, which is the same maximum dose also applied in the parent studies.

Osilodrostat (LCI699) will be given in form of film-coated tablets for oral administration, and available in the following dose strengths: 1 mg, 5 mg and 10 mg.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Not applicable.

4.4 Purpose and timing of interim analyses/design adaptations

Not applicable.

4.5 Risks and benefits

There is still an unmet need in the treatment of CD: despite available therapies, a substantial number of subjects do not achieve normalization of cortisol, lose biochemical control over time or present medication-related adverse reactions and may stop treatment because of this.

In order to mitigate the potential risks related to the administration of osilodrostat, some procedures will be taking place:

- The starting dose should be the same as the dose provided in the parent osilodrostat study at the time of transition to the roll-over study. However, the investigator can change the dose based on the subject's response; the maximal dose should not exceed 30 mg b.i.d.
- Subjects will be evaluated by the treating investigator for clinical benefit and safety based on the following assessments:
  - Physical examination (every 12 weeks)
  - Body weight / blood pressure (every 12 weeks), 12-lead safety ECG (every 24 weeks), blood chemistry and hematology (every 24 weeks), 11-deoxycortisol and 11 deoxycorticosterone (every 24 weeks), testosterone (every 24 weeks), Urinary Free Cortisol (UFC) (every 12 weeks), serum cortisol as clinically indicated, plasma ACTH (every 12 weeks) and pituitary MRI (every 48 weeks or more frequently if clinically needed).
- AEs and SAEs will be reported continuously and evaluated by the investigator at each visit.
- Drug administration record for dosing of osilodrostat will be completed at baseline and during treatment visits.
- For females, urinary pregnancy test will be performed at each visit (every 12 weeks) and monthly, at home.
- Upon administration of the last drug dose, discontinuation from the study or study end, the patient will have a follow-up visit 30 days later.
- The protocol provides specific guidance for dose modifications and/or stopping rules, due to osilodrostat-related toxicities. In addition, a safety follow-up for liver toxicity and management of QT prolongation have also been included.

Potential subject benefits

There is an unmet medical need in subjects with CS since this is a rare and serious disease but with limited medical treatment options.

An open label, proof-of-concept, single-arm study (CLCI699C2201, LINC 2) has been conducted to assess the safety and tolerability of osilodrostat in patients with CD after 10 weeks of treatment.

In this study, 12 CD patients received osilodrostat orally for 10 weeks. The drug was given at the starting dose of 2 mg b.i.d., and was progressively increased on the basis of the urinary

cortisol levels till their normalization or a maximum dose of 50 mg b.i.d. was achieved. After 10 weeks of treatment, all 12 patients normalized urinary cortisol levels or achieved a > 50% reduction in urinary cortisol levels. The reduction of urinary cortisol levels was accompanied by a trend towards a decrease in BP. Osilodrostat was generally well tolerated, with the most frequently reported adverse events being fatigue (58.3%), nausea (41.7%), diarrhea (25%), headache (25%), hypokalemia (25%), muscle spasms (25%) and vomiting (25%).

Recently, an amended extension of the phase II study (CLCI699C2201, LINC 2) is currently ongoing with the overall objective of evaluating the efficacy and safety of osilodrostat for a longer period of time. After 22 weeks of treatment, 15 out of 19 patients (78.9%) had normalized UFC. The decrease in urinary cortisol levels was associated with improvements in the glucose and lipid profiles. Adverse events during this extension of the study included GI disturbances (nausea and diarrhea in 31.6%), asthenia (31.6%) and adrenal insufficiency (31.6%), together with an increase in ACTH, cortisol and aldosterone precursors, and an increase in testosterone, which, in some women was associated with onset or worsening of acne and hirsutism.

There was a trend toward improved fasting glucose and HbA1c in patients with diabetes at baseline, and an improved fasting lipid profile in patients with dyslipidemia at baseline.

After the initial 22 weeks (core study), patients were invited to enter the extension study up to month 31. Safety and efficacy results have shown that the drug's profile will fulfill the unmet need in the medical management of endogenous hypercortisolism because:

- Normal UFC was maintained for >2.5 years in a majority of patients.
- None of the patients with normalization of cortisol experienced escape from response
- Clinical measures improved, particularly body weight and BMI
- Occurrences of the most commonly reported AEs decreased over time

Therefore, osilodrostat seems to be a promising drug for the treatment of CD, with a satisfactory safety and tolerability profile.

Risks of osilodrostat treatment in study population

Known risks of treatment with LCI699 in patients with CS include: QT prolongation, hypocortisolism/adrenal insufficiency, AEs related to the accumulation of precursor molecules, including: increased or decreased blood pressure, hypokalemia or hyperkalemia, hyponatremia, weight gain, edema, and increase in the synthesis of sex steroids (primarily adrenal androgens in women) that may lead to menstrual changes and hirsutism in women and acne in either men or women. Skin rash has been observed. Corticotroph tumor progression, with or without compressive symptoms, is a potential risk.

Neutropenia has been observed in a small number of patients with CD receiving osilodrostat. Preliminary assessment suggests that these events might be associated with cortisol levels that are either below normal or have had a rapid and substantial decline from baseline. In the observed cases, neutropenia rapidly reverses either spontaneously (typically after dose decrease) or with discontinuation of osilodrostat.

In addition, the protocol provides specific guidance for safety follow-up for liver toxicity (increased transaminases, increased total bilirubin) and an algorithm for monitoring and management of QT prolongation.

Conclusion

The treatment of patients with CS still represents a challenge: the available treatments do not lead to biochemical control in quite a large number of patients and many of them lose biochemical control over time.

Therefore there is an unmet medical need to develop new drugs with improved safety, efficacy and a more patient-friendly profile.

Based on current safety and efficacy data of osilodrostat, the overall benefit-risk of trial participation is expected to be positive for all subjects to be enrolled in this study.

5 Population

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

5.1 Inclusion criteria

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

1. Patient is currently participating in a Global Novartis-sponsored study receiving osilodrostat for any type of endogenous CS and has fulfilled all their requirements in the parent study.
2. Patient is currently benefiting from treatment with osilodrostat, as determined by the Investigator.
3. Patient has demonstrated compliance, as assessed by the Investigator, with the parent study protocol requirements.
4. Willingness and ability to comply with scheduled visits and treatment plans.
5. Written informed consent obtained prior to enrolling into the roll-over study before evaluating the applicability of the subject's participating in the study.
    - If consent cannot be expressed in writing, it must be formally documented and witnessed, ideally via an independent trusted witness.

5.2 Exclusion criteria

Patients meeting any of the following criteria are not eligible for inclusion in this study.

1. Patient has been permanently discontinued from osilodrostat study treatment in a parent Novartis-sponsor study.
2. Patients who are receiving osilodrostat in combination with unapproved or experimental treatments for any type of endogenous CS.
3. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory evaluation.

Pregnant or nursing (lactating) women

4. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 1 week of study after stopping medication. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation. at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to baseline). The vasectomized male partner should be the sole partner for that subject
    - Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment, and must be used in combination with a barrier method (male condom).

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or total hysterectomy, or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment, it will be considered not of child bearing potential.

6 Treatment

Study treatment and investigational treatment refer to osilodrostat.

6.1 Study treatment

The study treatment consists of osilodrostat (LCI699), in the form of film-coated tablets for oral administration, in the following tablet strengths: 1 mg, 5 mg and 10 mg. Each strength has a unique size, color and imprint (Y1, Y2 and Y3) on each tablet which can be used for specific identification.

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply type	Sponsor (global or local)
Osilodrostat	Film-coated tablet up to 30 mg	Oral use	Open label bulk supply	Bulk product supplied by Novartis Finished product: supplied by IQVIA Vendor* or Novartis

* Upon sponsorship approval status

The starting dose of study treatment for patients in this study should be the same as the dose provided in the parent osilodrostat study at the time of transition to the roll-over study.

However, the investigator can change the dose and frequency of osilodrostat administration based upon the subject's response but should not exceed 30 mg b.i.d.

Study drug should be taken twice a day (b.i.d.). For example a subject on a 2 mg b.i.d. dose will take 2 mg in the morning and 2 mg in the evening, providing a total daily dose of 4 mg. Study drug should be taken at approximately the same time each day, with about 12 hours between each dose administration. Osilodrostat can be dosed without regard to food. If vomiting occurs during the course of treatment, patients should not take the study drug again before the next scheduled dose. Subjects should be instructed not to make up missed doses. A missed dose is defined as a case when the dose is not taken within 4 hours after the usual dosing time.

At every quarterly visit (every 12 weeks ± 2 weeks) patients will receive sufficient supply of osilodrostat to cover a period of at least 3 months until the next scheduled visit.

Subjects should be requested to bring their unused study drug, including the empty packs, to the clinic at each visit. Compliance should be verified and documented by the Investigator's staff by counting the number of dispersible tablets consumed between visits. The Investigator (or his/her designee) will document dosage administration and all dose changes during the study in the eCRF. The site must maintain an overall drug accountability log for the study, as well as individual accountability records for each patient. The dose, amount dispensed, amount received, and amount remaining unused must be recorded in the source document. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. The patient will return all unused study drug at each dispensing visit and at the end of the study.

6.1.2 Additional study treatments

Not applicable.

6.1.3 Treatment arms/group

Subjects will receive the same dose as the dose provided in the parent osilodrostat study at the time of transition to the roll-over study.

6.1.4 Guidelines for continuation of treatment

Osilodrostat therapy is continued unless it must be interrupted or discontinued for safety or other reasons. See Section 6.5 for details.

6.1.5 Treatment duration

The study is expected to remain open for approximately 5 years (or until 31-December-2023 in the UK) from FPFV. Subjects will continue to be treated in the roll-over study until they are no longer benefiting from their osilodrostat treatment as judged by the Investigator or until osilodrostat is commercially available or until one of other discontinuation criteria is met (please refer to Section 9.1.1). At every quarterly visit (every 12 weeks ± 2 weeks), the Investigator is required to confirm that the subject continues to have clinical benefit and can continue receiving study treatment. A subject will reach the end of the roll-over study when osilodrostat treatment is permanently discontinued.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

Stable doses of concomitant medications (except those for hypercortisolism) are allowed during the study. All pre-existing concomitant medications should be recorded at study start. The investigator should instruct the subject to notify the study site about any new medications he/she takes after the start of the study. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject signs the informed consent must be documented at the study site.

6.2.1.1 Permitted concomitant therapy

The subject must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be documented at the study site.

6.2.1.2 Permitted concomitant therapy requiring caution and/or action

Spironolactone and eplerenone are permitted for the treatment or prevention of study drug-related edema or hypokalemia. The use of these drugs should be done with close monitoring for the potential risk of severe hyperkalemia, which is further increased if renal insufficiency is present.

Spironolactone, cyproterone acetate or finasteride for treatment of hirsutism are approved in some countries and are not prohibited.

Medications that are metabolized by CYP450 enzymes

In vitro drug metabolism studies show that LCI699 is a potential inhibitor of CYP1A2, CYP2C19, CYP2D6, CYP3A4/5 and CYP2E1, and may consequently increase exposure to drugs metabolized by this enzyme.

In a clinical DDI study, LCI699 was found to be a moderate inhibitor of CYP1A2 (2.5-fold increase in substrate exposure), a weak to moderate inhibitor of CYP2C19 (1.9-fold increase in substrate exposure), and a weak inhibitor of CYP2D6 and CYP3A4/5 (1.5-fold increase in substrate exposure). Therefore concomitant medications that are known substrates of these enzymes (see Appendix 1) and which have a narrow therapeutic index should be used with caution.

The subject and the Investigator should be aware of potential signs of overdose of the concomitant medication and in the event of suspected toxicities; administration of either the substrate or LCI699 should be discontinued according to Investigator's judgment.

6.2.2 Prohibited medication

Use of the following concomitant medication is prohibited during the study:

- Other drug treatments for CD or CS;
- Medications with a "known risk to cause Torsades des Pointes (TdP)" and "possible risk to cause TdP";
- Eplerenone and glucocorticoids, except under certain conditions:
  - Eplerenone may be used if necessary in acute post-myocardial infarction management, and in the event of refractory hypokalemia in patients with hypertension or edema; glucocorticoids may be used as required for the short-term treatment of hypocortisolism or adrenal insufficiency.
  - Glucocorticoids (e.g., prednisone, prednisolone, and dexamethasone) may be used as required for the short-term treatment of hypocortisolism or adrenal insufficiency. If glucocorticoids are used in stress doses, or as replacement therapy, for > 4 weeks, then the investigator should consider temporary interruption of LCI699, weaning and discontinuation of glucocorticoid therapy, or early discontinuation from the study.

6.2.2.1 Concomitant medications with a "Known risk to cause TdP" and with a "Possible risk to cause TdP".

Preclinical and clinical data indicate that there is a risk of QTc prolongation in humans (see Section 6.5.1.2). Therefore, the use of medications with a "known risk to cause TdP" and with a "possible risk to cause TdP" concomitantly with LCI699 is prohibited. If a subject requires a long-term medication from the two categories mentioned above, and there is no appropriate alternative medication available, they should be discontinued from the study.

However, if a subject requires such a drug for short-term therapy, e.g., antibiotics for active infection, then the LCI699 treatment may be interrupted temporarily while this drug is administered after a thorough risk-benefit assessment. This does not require the subject to discontinue from the study prematurely. Washout periods for LCI699 and the short-term prohibited drug in many cases may not be possible; this is acceptable if the benefit of the drug outweighs the risk of withholding LCI699 therapy in the investigator's judgment. In such cases, a discussion with the Recordati Medical Monitor is recommended.

Please refer to Section 14.2 Appendix 2 for an e-link to a list of medications that have a "known risk to cause TdP" and "possible risk to cause TdP". Investigators are advised to

utilize this website when considering the addition of a new concomitant medication, as the lists are periodically updated. If necessary, a discussion can be held with the Recordati Medical Monitor when considering the use of medications with a "known risk to cause TdP" and with a "possible risk to cause TdP" A list of drugs with a "known risk to cause TdP" and with a "possible risk to cause TdP" can be found at crediblemeds.org\

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

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

6.3.2 Treatment assignment, randomization

All consented subjects who satisfy all the inclusion and exclusion criteria, are eligible to receive osilodrostat.

6.4 Treatment blinding

Not applicable.

6.5 Dose modification

6.5.1 Dose modifications

6.5.1.1 Dose modification and dose delay

The osilodrostat dose should be adjusted until normalization of cortisol. The treating physician can increase the dose as needed, up to 30 mg b.i.d.

For subjects who are unable to tolerate the current dose, dose adjustments can be done at investigator's discretion. The guidelines below may be followed:

- If the subject has not reached normalization of cortisol, but does not tolerate the current dose, administration of an intermediate dose (between the current and preceding dose) or repeated administration of the preceding, tolerated dose should be considered.
- If the subject has reached normalization of cortisol, but the current dose is no longer tolerated, an intermediate dose between the current dose and previous dose should be considered.
- If the subject had reached normalization of cortisol, but the current dose is no longer efficacious based on cortisol measurements, dose escalation should resume.

- If the subject has low serum cortisol < LLN, and the patient has signs/symptoms of cortisol-withdrawal syndrome or adrenal insufficiency, a dose reduction of LCI699 should be considered.

Any dose changes must be recorded on the Dosage Administration Record eCRF.

At the time of the next study visit, the patient must:

- Return all unused tablets to the site for drug accountability.
- The IRT system specifies which study drug packs are to be dispensed to the patient. **It is very important** for the site personnel and the subject to be aware that it is possible that more than one tablet strength may be dispensed at the same visit.
- Receive instructions on how to administer the dose and dosing schedule.

Additional dose modifications guidance is summarized in Table 6-2. Deviations to mandatory dose interruptions and/or reductions are not allowed. Permanent treatment discontinuation is mandatory for specific events indicated as such in Table 6-2 or listed in Section Section 9.1.1.

Table 6-2 Dose Modification Guidelines for osilodrostat-suspected toxicities

Toxicity	Suggested Actions
Symptomatic hypocortisolism or adrenal insufficiency	If the investigator at any time suspects hypocortisolism or adrenal insufficiency, they can immediately interrupt study drug and initiate replacement with glucocorticoids. Upon recovery as assessed by the investigator, glucocorticoid therapy can be tapered as tolerated, and study drug can be re-started. The decision to restart study drug will be made by the investigator. The AE and associated treatments with changes to study drug need to be appropriately documented in the eCRF. Recovery is assessed clinically by the investigator. A general guideline is that glucocorticoid taper can begin when cortisol in the upper part of the normal range or > ULN*, and study drug can be re-started if the patient is clinically stable off glucocorticoid therapy for at least one week, and the cortisol is normal or > ULN.
Persistent asymptomatic hypocortisolism (cortisol < LLN) at the lowest dose of LCI699 (1 mg every other day)	The investigator can interrupt study drug and restart at the same dose as clinically indicated.
Glucocorticoid withdrawal syndrome	Reduce or withhold dose until improved
*Hypotension (mild, reversible)	Reduce or withhold dose until improved
*Hypertension	Reduce or withhold dose until improved; consider angiotensin-converting-enzyme (ACE) inhibitors if appropriate for treatment of hypertension, or spironolactone as a second line treatment, particularly if hypokalemia is present. ACE inhibitors and spironolactone should not be used in combination.
*Weight gain, edema	Reduce or withhold dose until improved; consider spironolactone for treatment of edema.
*Hypokalemia	Consider reducing or withholding dose until improved; replace potassium; consider spironolactone or eplerenone for prevention and treatment of hypokalemia
*Hyperkalemia	Consider reducing or withholding dose until improved; if on spironolactone or eplerenone, reduce or withhold; treat with kayexalate and other potassium lowering therapies as needed.

Toxicity	Suggested Actions
*Hirsutism (women only)	Reduce or withhold dose until improved; review testosterone level; consider spironolactone, cyproterone acetate or finasteride per local guidelines.
*Acne (women or men)	Reduce or withhold dose until improved; review testosterone level; consider spironolactone, cyproterone acetate or finasteride per local guidelines.
* Abbreviations: ULN, upper limit of the normal reference range; LLN, lower limit of the normal reference range; ACE, angiotensin-converting-enzyme.	

It is expected that subjects will be seen urgently in an unscheduled visit at the site in the event of signs/symptoms of suspected hypocortisolism or adrenal insufficiency or any other AE that requires study drug interruption with or without glucocorticoid therapy.

However, there may be occasions in which the subject has been seen at another health care facility, or has called in to report symptoms; in these cases, subjects should be advised to come to the site as soon as possible if it is safe, or go to the nearest hospital emergency room.

In addition, any AE, regardless of suspected drug causality, may require interruption of osilodrostat and replacement or stress doses of glucocorticoid therapy until resolution of the event.

- Upon recovery from the AE, the investigator may consider re-starting osilodrostat if the dose interruption has been ≤ 14 days.
- If the dose interruption has been > 14 days, then the subject should be observed. If cortisol rises to above the ULN, and has been off glucocorticoid therapy for at least one week, osilodrostat may be re-started.

Table 6-3 Criteria for interruption and re-initiation of osilodrostat for abnormal liver function

Isolated total Bilirubin elevation	
> ULN – 1.5 x ULN	Maintain dose level
> 1.5 - 3.0 x ULN	Withhold study drug. Monitor liver function tests (LFT)[a] weekly , or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN: If resolved in ≤ 14 days, then maintain dose level If resolved in > 14 days, then decrease by one dose level.
> 3.0 - 10.0 x ULN*	Withhold study drug. Monitor LFTs[a] weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN: If resolved in ≤ 14 days, then decrease by one dose level. If resolved in > 14 days, then discontinue patient from study drug treatment. The patient should be monitored weekly (including LFTs[a]), or more frequently if clinically indicated, until total bilirubin has returned to baseline or stabilized over 4 weeks.
> 10.0 x ULN*	Discontinue patient from study drug treatment The patient should be monitored weekly (including LFTs[a]), or more frequently if clinically indicated, until total bilirubin has returned to baseline or stabilized over 4 weeks.
Isolated AST or ALT elevation	
> ULN - 3.0 x ULN	Maintain dose level
> 3.0 - 5.0 x ULN	Maintain dose level. Repeat LFTs[a] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs[a] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN

> 5.0 - 10.0 x ULN	Withhold study drug. Repeat LFTs[a] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[a] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN. Then: If resolved in ≤ 14 days, restart study drug and maintain dose level If resolved in > 14 days, restart study drug and decrease dose by one level If not resolved after 4 weeks, discontinue patient from study treatment
> 10.0 x ULN	Permanently discontinue study drug. Repeat LFTs[a] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[a] weekly, or more frequently if clinically indicated, until resolved to ≤3 x ULN.
Combined [b, c] elevations of AST or ALT and total bilirubin	
For patients with normal baseline ALT and AST and total bilirubin value: AST or ALT >3.0 x ULN combined with total bilirubin >2.0 x ULN without evidence of cholestasis[c] OR For patients with elevated baseline AST or ALT or total bilirubin value: [AST or ALT>2x baseline AND > 3.0 xULN] OR [AST or ALT > 8.0 xULN], combined with [total bilirubin >2x baseline AND >2.0 xULN	Permanently discontinue patient from study drug treatment. Repeat as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs[a], or more frequently if clinically indicated, until AST, ALT, or bilirubin have returned to baseline or stabilized over 4 weeks. Refer to Section 6.5.3 for additional follow-up evaluations as applicable.
All dose modifications should be based on the worst preceding toxicity. Core LFTs consist of ALT, AST, GGT, total bilirubin (fractionated [direct and indirect], if total bilirubin > 2.0 x ULN), and alkaline phosphatase (fractionated [quantification of isoforms], if alkaline phosphatase > 2.0 x ULN.) "Combined" defined as: total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold. If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of total bilirubin and isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g. discontinue treatment at the situation when omit dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start the treatment either at the same dose or at one dose lower if meeting a criterion for dose reduction "Cholestasis" defined as: ALP elevation (>2xULN and R value (ALT/ALP in x ULN) < 2). Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury *Note: If total bilirubin > 3.0 x ULN is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level and continue treatment at the discretion of the investigator.	

If the subject has interruption of osilodrostat for more than 4 weeks, the investigator should consider early discontinuation from the study.

6.5.1.2 Follow-up for QT prolongation

In the event that QT prolongation is detected during routine investigation, the following guidance is provided to be followed by the investigator:

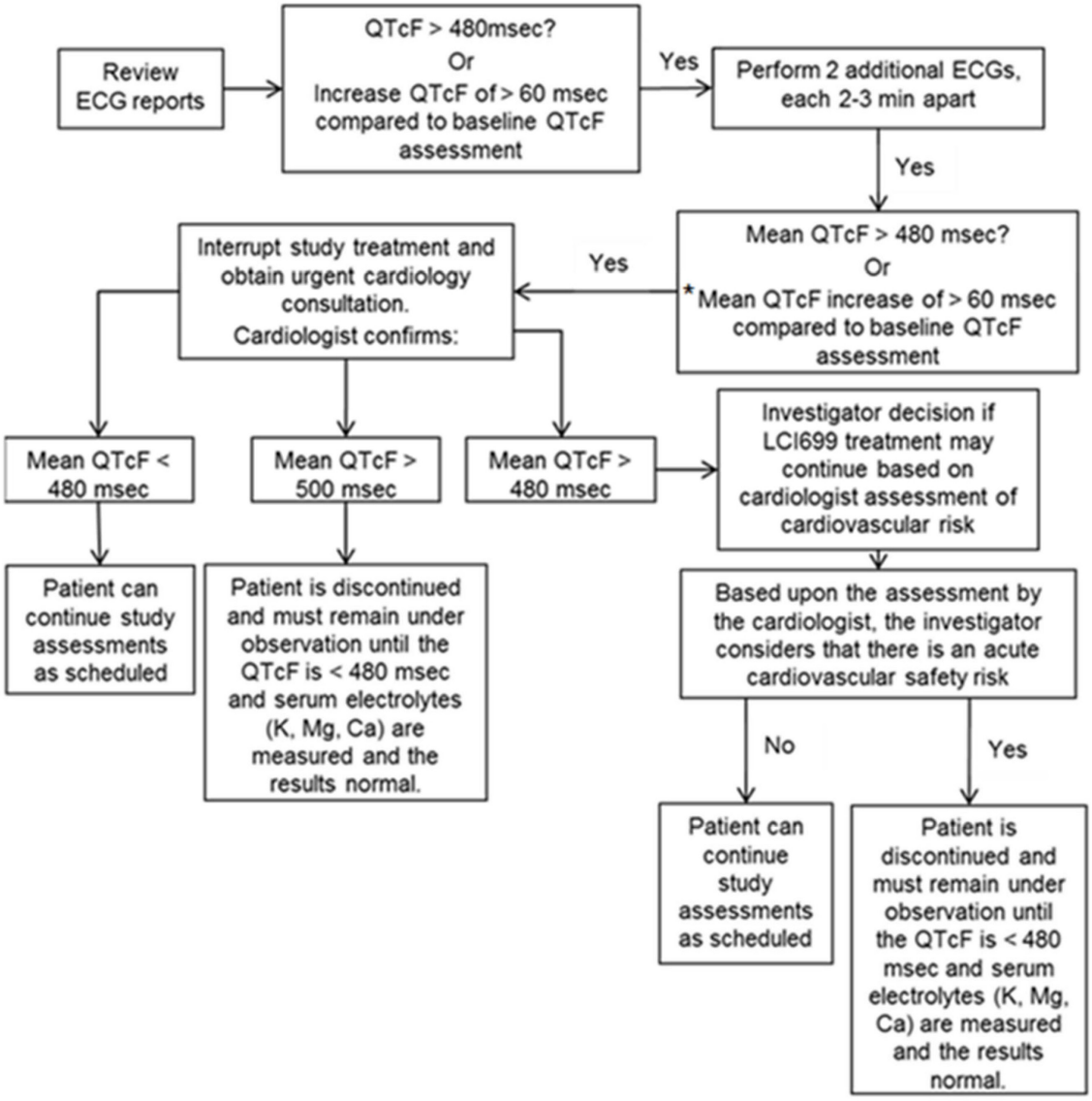
- If a QTcF > 480 msec is observed or an increase of the QTcF of >60 msec compared to baseline QTcF assessment of the roll-over, then two additional ECGs, each 2-3 minutes apart, need to be taken after the initial ECG. The mean QTcF from the triplicate ECGs will be determined. If the mean QTcF is > 480 msec or the mean QTcF increase is >60 msec compared to baseline, the patient has to interrupt study treatment while an urgent cardiology

consultation is obtained to re-evaluate the ECG and perform a clinical consultation. If immediate treatment is required for subject safety, this should be initiated at the study site without delay and without waiting for confirmation by a cardiologist.

Based on the cardiologist consultation, the following should occur:

- If a mean QTcF > 480 msec is NOT confirmed, no further action needs to be taken.
- If the cardiologist confirms a mean QTcF > 500 msec, the subject has to discontinue according to the discontinuation procedure described in Section 9.1.1. The subject must remain under observation until the QTcF is < 480 msec and serum electrolytes, calcium, and magnesium are measured and the results normal. This observation may be done at the site, in an Emergency Room, or a cardiology clinic, as appropriate and depending upon local resources.
- If the cardiologist confirms that QTcF > 480 msec, osilodrostat treatment is temporarily interrupted and a thorough evaluation is performed to assess the patient for acute cardiovascular risk, and for possible underlying heart disease that needs additional evaluation and management.
  a. If based upon the assessment by the cardiologist, the investigator considers that there is an acute cardiovascular safety risk and that the patient should not continue with:study medication, the patient needs to be discontinued immediately (discontinuation criteria described in Section 9.1.1).
  b. If based upon the assessment by the cardiologist, the investigator considers that there is not an acute cardiovascular safety risk; the patient can continue to receive study medication.

Figure 6-1 QT monitoring Flow Chart



* Please refer to Section 9.1.1, study treatment must be discontinued under this circumstance.

6.5.2 Follow-up for toxicities

Please refer to Section 6.5.1.

6.5.3 Follow up for potential drug-induced liver injury (DILI) cases

In the event that concomitant aminotransferase and bilirubin elevations are detected during routine investigation, the following guidance is provided to be followed by the investigator.

Patients with transaminase increase combined with TBIL increase may be indicative of potential DILI, and should be considered as clinically important events.

The threshold for potential DILI may depend on the patient's baseline AST/ALT and TBIL value; patients meeting any of the following criteria will require further follow-up as outlined below:

- For patients with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN
- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as ALP elevation > 2.0 x ULN with R value < 2 in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis.

In the absence of cholestasis, these patients should be immediately discontinued from study drug treatment, and repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory evaluations, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

1. Laboratory evaluations should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR and alkaline phosphatase.
2 . A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.
3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.
4. Obtain PK sample, as close as possible to last dose of study drug, if PK analysis is performed in the study.
5. Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as "medically significant", thus, met the definition of SAE (Section 10.1.2) and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

The investigator must promote compliance by instructing the subject to take the study treatment exactly as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study. The subject must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts (if applicable) and information provided by the subject. This information should be captured in the source

document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

6.6.2 Emergency breaking of assigned treatment code

Not applicable.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section.

Investigator staff will identify the study medication kits to dispense to the subject by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the subject, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

6.7.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the [Investigator's Brochure]. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to Recordati Quality Assurance.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Subjects will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the CRO monitor or to the address provided by Recordati or the CRO in the investigator folder at each site.

7 Informed consent procedures

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

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

CRO on behalf of Recordati will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Recordati before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB. This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the subject.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

A copy of the approved version of all consent forms must be provided to the sponsor after IRB/IEC approval.

8 Visit schedule and assessments

Assessment schedule lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the subject’s source documentation.

Subjects should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event recorded on the CRF.

Table 8-1 Assessment Schedule

Visit Name	Category	Protocol Section	Baseline / Enrollment	Visits during Treatment (Week 12 and every 12 weeks (+/- 2 weeks) thereafter)					End of study treatment (EoT)	30 day safety follow-up post last dose of study drug / End of Study
			W1D1	W12D1	W24D1	W36D1	W48D1	W60D1 Onwards	EOT	N/A
Visit Number			1	110	120	130	140	150	1999	FU
Obtain informed consent	D	7	x							
Study History	D	8.2	x							
Demography	D	8.2	x							
Medical History	D	8.2	x							
Inclusion/exclusion criteria	D	5.1	x							
Blood chemistry	D	8.4.3	x		x		x		x	x
Hematology	D	8.4.3	x		x		x		x	x
Physical examination	S	8.4.1	x	x	x	x	x	x	x	x
Body weight / blood pressure	D	8.4.2	x	x	x	x	x	x	x	x
UFC (two 24-h specimens)	D	8.4.3	x	x	x	x	x	x	x	x
Plasma ACTH	D	8.4.3	x	x	x	x	x	x	x	x
11-deoxycortisol and 11 deoxycorticosterone, testosterone	D	8.4.3	x		x		x		x	x
12 Lead safety ECG assessment	D	8.4.4	x		x		x		x	x
Pituitary MRI	D	8.4.6	x				x		x	
Urine pregnancy testing (if positive, serum pregnancy test required) – WOCBP only	S	8.4.5	x	At every visit and monthly (at home)					x	x
Adverse events and Serious adverse events	D	10.1	x	continuous						
Osilodrostat drug administration record	D	6.1	x	continuous						

Visit Name	Category	Protocol Section	Baseline / Enrollment	Visits during Treatment (Week 12 and every 12 weeks (+/- 2 weeks) thereafter)					End of study treatment (EoT)	30 day safety follow-up post last dose of study drug / End of Study
			W1D1	W12D1	W24D1	W36D1	W48D1	W60D1 Onwards	EOT	N/A
Confirmation of Clinical Benefit from Study Treatment	D	6.1.5	x	x	x	x	x	x	x	
End of phase disposition	D	9.1.1							x	

8.1 Screening

Molecular pre-screening

Not applicable.

Screening

At the enrollment visit the patient will complete a written informed consent. There will be no screening period for this study, this will be referred to as Baseline. Once consented, patients will be evaluated for eligibility via the inclusion and exclusion criteria.

8.1.1 Information to be collected on screening failures

Not applicable.

8.2 Subject demographics/other baseline characteristics

Country specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF

8.3 Efficacy

8.3.1 Efficacy assessments

At every 12 week-visit (± 2 weeks), the Investigator is required to confirm that the patient continues to have clinical benefit and may continue receiving study treatment.

8.3.2 Appropriateness of efficacy assessments

Due to the nature of the roll over, only clinical benefit will be assessed.

8.4 Safety

Safety assessments are specified in the assessment schedule, Table 8-1.

For details on AE collection and reporting, refer to AE section.

Safety assessments as specified below must be maintained in source documentation for each patient in the study consisting of case and visit notes (hospital or clinical medical records) as well in the clinical DB according to table 8.1. Letter “D” indicates which safety assessments should be recorded in eCRF and/or vendor DB and letter “S” indicates that the assessments should be recorded in site source patient data.

At baseline visit, the data for all assessments (except Obtain inform consent, Confirmation of Clinical Benefit from Study Treatment, and End of phase disposition) will be taken from the parent study.

8.4.1 Physical Examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, and extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and/or pelvic exams may be performed. This will be conducted at visits according to the Assessment schedules.

Significant findings that are present prior to joining this study must be included in the Relevant Medical History/Current Medical Conditions screen on the patient's eCRF. Significant findings made after the start of study drug which meet the definition of an Adverse Event must be recorded on the Adverse Event screen of the patients eCRF.

8.4.2 Body weight and blood pressure

Body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured. Body weight will be measured at visits according to the Assessment schedules.

After the patient has been sitting for 3 minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using an automated validated device, with an appropriately sized cuff. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

Blood pressure will be measured at visits according to the Assessment schedules.

Body weight and blood pressure should be recorded in eCRF.

8.4.3 Laboratory evaluations

All laboratory evaluations will be performed using central laboratory according to the Assessment schedule: blood chemistry (Albumin, alkaline phosphatase, total bilirubin, calcium, creatinine, CK, GGT, inorganic phosphorus, lipase, amylase, magnesium, potassium, total protein, AST, ALT, sodium, urea/BUN and uric acid, HbA1c), hematology (Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, (monocytes, eosinophils, basophils, neutrophils, lymphocytes), and platelet count), testosterone, serum cortisol as clinically indicated, urine free cortisol (two 24-hour urine specimens collected), plasma ACTH, 11-deoxycortisol and 11 deoxycorticosterone.

8.4.4 Electrocardiogram (ECG)

Twelve-lead safety ECGs are collected at the study site using ECG equipment available at the sites. This ECG must be read on site by a qualified physician (e.g., the investigator, or another qualified physician such as a consulting cardiologist) on the day they are collected and recorded in eCRF for each patient.

Only ECGs with clinically significant ("notable") abnormalities should be reported as AE. A "notable abnormality" is defined as:

- QTcF > 480msec with acute cardiovascular risk, as assessed by a consulting cardiologist
- Any QTcF > 500msec, confirmed by a consulting cardiologist

- QTcF increase > 60 msec from baseline.

The frequency of the ECG assessment is provided in Table 8-1.

8.4.5 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Pregnancy test will be performed as detailed in the assessment schedule Table 8-1.

Assessments of Fertility

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child bearing potential must also be available as source documentation in the following cases:

1. surgical bilateral oophorectomy without a hysterectomy
2. reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH testing is required of any female subject, regardless of reported reproductive/menopausal status at screening/baseline.

8.4.6 Pituitary scan

Pituitary MRI scanning with gadolinium enhancement will be performed every 48 weeks or more frequently if clinically needed at visits according to the assessment schedule provided in Table 8-1 using the local site facility. These will be assessed locally to determine the longest diameter and the tumor volume. For MRI (or CT) images that are not interpretable for tumor volume, the longest dimension (in mm) will be summarized instead. If MRI intravenous contrast is contraindicated for a patient, a non-contrast MRI scan should be performed. If MRI cannot be performed at all then a CT (with i.v. contrast if not contraindicated) may be performed. Digital images are to be kept at the site in the event Recordati requests transfer of the files at a later date. The Pituitary MRI scanning should be recorded in eCRF.

8.4.7 Appropriateness of safety measurements

The safety assessments are standard for this indication/subject population.

8.5 Additional assessments

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

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration, and can be initiated by either the subject or the investigator.

The investigator must discontinue study treatment for a given subject if, he/she believes that continuation would negatively impact the subject's well-being. Study treatment must be discontinued under the following circumstances:

- Emergence of the following adverse events:
  - Hypertension defined as office mean sitting systolic BP> 180 mmHg or mean sitting diastolic BP> 110 mmHg (confirmed and persistent, persistent is defined as unresolved with osilodrostat dose and/or other concomitant medication changes)
- Any of the following laboratory abnormalities (confirmed):
  - Hyperkalemia (serum potassium > 6.0 mmol/L).
  - Hypokalemia (serum potassium <2.8 mmol/L).
- Any of the following laboratory abnormalities (confirmed and persistent):
  - Hyperkalemia (serum potassium > 5.5 mmol/L).
  - Hypokalemia (serum potassium <3.0 mmol/L).
  - Hyponatremia (serum potassium <130 mmol/L).
  - AST or ALT >3.0 x ULN combined with total bilirubin >2.0 1 ULN without evidence of cholestasis.
- QTcF > 500 msec, if confirmed by a cardiologist (see Section 6.5.1.2),
- QTcF > 480 msec or QTcF increase is >60 msec compared to baseline if the investigator determines it is no longer safe for the patient to continue in the study, based on ECGs, cardiac examination, and recommendation from a cardiologist.
- Pituitary tumor growth, if the tumor is < 2mm from the optic chiasm, or symptoms of actual compression of the optic chiasm emerge (visual field loss, cranial nerve palsies, diplopia) confirmed by MRI of the pituitary.
- Protocol deviations
- Lost to follow-up
- Study terminated by the sponsor
- Administrative problems
- Physician decision
- Subject/guardian withdraw consent
- Subject has completed treatment based on study duration

  When current treatment becomes commercially available in the applicable country, the patient will be withdrawn from the study.
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Any situation in which study participation might result in a safety risk to the subject

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the subject’s premature discontinuation of study treatment and record this information.

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see withdraw of informed consent section,). **Where possible, they should return for the assessments indicated** in the assessment schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

If the subject cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject. This telephone contact should preferably be done according to the study visit schedule.

The investigator must also contact the IRT to register the subject's discontinuation from study treatment.

9.1.2 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Recordati will continue to retain and use all research results (data) that have already been collected for the study evaluation.

9.1.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed.

9.1.4 Early study termination by the sponsor

The study can be terminated by Recordati at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Recordati will always consider the subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible (provide instruction for contacting the subject, when the subject should stop taking drug, when the subject should come for a final visit) and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes their Study Completion visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

All treated subjects should have a safety follow-up call conducted 30 days after last administration of study treatment. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3. Documentation of attempts to contact the subject should be recorded in the source documentation.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual subject and identifying adverse events.

Recordati qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory evaluation findings, or other assessments.

Adverse events must be recorded under the signs, symptoms or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The [severity grade OR the Common Toxicity Criteria (CTC) AE grade (version 4.3 or higher)]

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

2. its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected'. The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding with study treatment.

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/withdrawn

6. its outcome i.e., its recovery status or whether it was fatal

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

Conditions that were already present at the time of informed consent should be recorded in medical history of the subject.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

Information about adverse drug reactions for the investigational drug can be found in the Investigator Brochure (IB).

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms

- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in subjects with the underlying disease.

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - social reasons and respite care in the absence of any deterioration in the subject's general condition
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant". Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the patient has stopped study treatment must be reported to IQVIA within 24 hours of learning of its occurrence. IQVIA, in its turn, will promptly inform Recordati. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

The date of the informed consent signed for this roll-over study (the roll-over date) is important to determine how SAEs should be reported:

- Any SAEs occurred prior to that date should be reported for the parent protocol, including all the follow up information relevant to such SAEs.
- New SAEs with an onset date on or after the roll-over date will be reported for this protocol.

It is important to use the right SAE form with the correct protocol number for these two scenarios, to avoid confusion in SAE processing. For a patient already on the roll-over protocol but follow up information is reported for the previous SAEs in the parent protocol, it must be clearly labeled that this is for the parent protocol number.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, IQVIA (in agreement with Recordati) may urgently require further information from the investigator for health authority reporting. IQVIA (on behalf of Recordati) may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30 day period after end of treatment should only be reported to IQVIA Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

Pregnancies

To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to IQVIA (which in turn will promptly inform Recordati) within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to IQVIA (which in turn will promptly inform Recordati). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Newborn of a patient who becomes pregnant during the study should be followed for 12 months post-delivery (from Day 0 to Month 12 of life).

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, subject or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the, respective sections.

10.2 Additional Safety Monitoring

Not applicable.

11 Data Collection and Database management

11.1 Data collection

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

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

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

11.2 Database management and quality control

Recordati personnel (or designated CRO, IQVIA) 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.

Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Data about all study treatment (s) dispensed to the subject and all dosage changes will be tracked using an Interactive Response Technology (IRT).

Once all the necessary actions have been completed and 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 after written agreement by Recordati development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, an IQVIA representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, IQVIA employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for

according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized IQVIA/CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to IQVIA clinical teams to assist with trial oversight.

The investigator must maintain source documents for each subject 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 on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. IQVIA monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12 Data analysis and statistical methods

12.1 Analysis sets

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

12.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients who receive at least one dose of study medication after enrolling into the roll-over study.

12.1.2 Safety set

The Safety Set includes all patients who received at least one dose of study medication after enrolling into the roll-over study. For this study, the definition of FAS is the same as the safety set.

12.1.3 Per-Protocol set

Not applicable.

12.1.4 Dose-determining analysis set

Not applicable.

12.1.5 Pharmacokinetic analysis set

Not applicable.

12.1.6 Other analysis sets

Not applicable.

12.1.6.1 Efficacy/evaluable set

Not applicable.

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

Relevant medical histories and current medical at baseline will be summarized by system organ class and preferred term.

12.3 Treatments

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure (week) to osilodrostat, the highest dose/average dose/dose with longest duration (from each individual patients) during the study and the dose level by visit (summary statistics of dose level among existing patients at a given visit) will be summarized by means of descriptive statistics. Boxplots for dose level by visit will be provided.

The number of patients with dose adjustments (reductions, interruption, or permanent discontinuation) and the reasons will be summarized and all dosing data will be listed.

12.4 Analysis of the primary endpoint(s)

12.4.1 Definition of primary endpoint(s)

The primary objective is to evaluate long term safety as assessed by the occurrence of AEs/SAEs.

12.4.2 Statistical model, hypothesis, and method of analysis

No hypothesis will be tested.

12.4.3 Handling of missing values/censoring/discontinuations

Not applicable.

12.4.4 Sensitivity and Supportive analyses

Not applicable.

12.5 Analysis of secondary endpoints

The secondary efficacy objective of the study is to evaluate clinical benefit as assessed by the Investigator. Proportions of patients with clinical benefit as assessed by the Investigator will be summarized at scheduled visits. Categorical data will be presented as frequencies and percentages.

The secondary safety objective of the study is to evaluate long term safety, assessed using laboratory data, vital signs (blood pressure and body weight), ECG and pituitary MRI. Details of the specific analyses for each type of safety endpoint is given in Section 12.5.1.

12.5.1 Safety endpoints

12.5.1.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used.

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

1. on-treatment period: from day of first dose of study medication in this study to 30 days after last dose of study medication
2. post-treatment period: starting at day 31 after last dose of study medication.

12.5.1.2 Adverse events (AEs)

Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period, the ***treatment-emergent*** AEs.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment.

Serious adverse events, non-serious adverse events during the on-treatment period will be tabulated.

All deaths (on-treatment and post-treatment) will be summarized.

All AEs, deaths and serious adverse events (including those from post-treatment periods) will be listed and those collected during post-treatment period will be flagged.

12.5.1.3 Laboratory abnormalities

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

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 evaluations where grades are not defined by CTCAE v4.03, results will be categorized as low/normal/high based on laboratory normal ranges.

Laboratory data will be listed and summarized as appropriate. Details of specific analyses will be given in the Statistical Analysis Plan.

12.5.1.4 Other safety data

Vital signs

Vital signs (BP and body weight) will be listed and summarized as appropriate. Details of specific analyses will be given in the Statistical Analysis Plan.

Pituitary MRI

Tumor volume and longest dimension will be evaluated as defined in Section 8.4.6

The longest dimension (in mm) and tumor volume (if evaluated) will be will be listed and summarized as appropriate. Details of specific analyses will be given in the Statistical Analysis Plan.

12.6 Analysis of exploratory endpoints

Not applicable.

12.7 Interim analyses

No formal interim analysis is planned for this study. Interim analysis may be performed for regulatory purposes if deemed necessary.

12.8 Sample size calculation

Not applicable.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to IQVIA monitors, auditors, Recordati/ Quality Assurance representatives, designated agents of

Recordati, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform IQVIA (and in turn Recordati) immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (**defined as last patient last visit**) and finalization of the study report the results of this trial will be disclosed to Competent Authorities, Ethics Committees and Investigators, submitted for publication and posted in a publicly accessible database of clinical trial results, such as Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

In accordance with Recordati publication policy, multicenter studies should be submitted for publication in peer-reviewed journals before, or in parallel with, any secondary publication (e.g. subgroups analyses or results from individual centers). A coordinating investigator will be designated by mutual agreement. Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.
In order to protect proprietary information and to provide comments, Recordati reserves the right to review all manuscripts and abstracts before their submission for publication or presentation at scientific meetings.

13.4 Quality Control and Quality Assurance

Recordati maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and CRO systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Recordati processes.

Recordati will ensure that the CRO has in place its own Quality Management System to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to

Recordati and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Recordati and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

14.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Recordati, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for subject safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, IQVIA (and in turn Recordati) should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

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16 Appendices

16.1 Appendix 1: List of drugs to be used with caution with LCI699

Osilodrostat should be used with caution when co-administered with CYP1A2 and CYP2C19 substrates with a narrow therapeutic index such as theophylline, tizanidine and mephenytoin.

Please refer to Section 5.1.5 of the current IB for further information".

16.2 Appendix 2: Medications with a "Known risk to cause TdP" and with a "Possible risk to cause TdP"

The following e-link provides a list of medications with a "known risk to cause TdP" and with a "possible risk to cause TdP". These medications are prohibited to be used concomitantly with LCI699: crediblemeds.org.

Investigators are advised to utilize this website when considering the addition of a new concomitant medication, as the lists are periodically updated. If necessary, a discussion can be held with the Recordati Medical Monitor when considering the use of medications with a "known risk to cause TdP" and "possible risk to cause TdP".