NOVARTIS

Clinical Development

Osilodrostat (LCI699)

Oncology Clinical Trial Protocol CLCI699C1201 / NCT02468193

A Phase II, open-label, dose titration, multi-center study to assess the safety/tolerability and efficacy of osilodrostat in patients with all types of endogenous Cushing's syndrome except Cushing's disease

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List of abbreviations

ACTH	Adrenocorticotropic Hormone
AE	Adverse Event
AESI	Adverse events of special interest
AIMAH	ACTH-Independent Macronodular Adrenal Hyperplasia
AIP	Aryl hydrocarbon receptor interacting protein
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
BDI®-II	Beck Depression Inventory®-II
b.i.d.	*bis in diem*/twice a day
BIPSS	Bilateral inferior petrosal sinus sampling
BMI	Body mass index
CD	Cushing's Disease
CMO&PS	Chief Medical Office and Patient Safety
CNS	Central Nervous System
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRH	Corticotropin Releasing Hormone
CRO	Contract Research Organization
CS	Cushing's Syndrome
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DDI	Drug-Drug interaction
DEX	Dexamethasone
DILI	Drug-Induced Liver Injury
ECG	Electrocardiogram
EEA	European Economic Area
EoT	End of Treatment
FSH	Follicle stimulating hormone
GDPR	General Data Protection Requirements
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
LDH	lactate Dehydrogenase
LFT	Liver Function Test
LH	Luteinizing Hormone
LLN	Lower Limit of Normal
LLOQ	Lower Limit Of Quantification
MAP	Master Analysis Plan documents project standards in the statistical methods which will be used within the individual clinical trial RAP documentation
(m)UFC	(mean) Urine Free Cortisol
pCO_2	Partial pressure of carbon dioxide
PHI	Protected Health Information
PK	Pharmacokinetic
p.o.	*per os*/by mouth/orally
PoC	Proof of Concept

[redacted]

ACTH	Adrenocorticotropic Hormone
PPNAD	Primary Pigmented Nodular Adrenal Dysplasia
QTcF	QT interval Corrected according to Friderica's formula
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
RBC	Red Blood Cells
REB	Research Ethics Board
RoW	Rest of World
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TBIL	Total Bilirubin
TdP	Torsades de Pointes
ULN	Upper Limit of Normal
WBC	White Blood Cells

[redacted]

Amendment 4 (31-Jul-2018)

Amendment rationale

Study status: As of 12 Jul 2018, 9 patients have been enrolled into the study, received study drug and only one patient continues study treatment. The study enrollment has been completed.

The data cut-off date for the primary analysis was 7 Jun 2018 when all 9 patients had completed study period I (Week 12). The primary analysis is on-going.

The main purpose of this amendment is to accommodate the remaining patient to be able to continue study treatment until the next surgery or local alternative treatment options is available beyond Week 72.

The other purpose of this amendment is to remove the planned second analysis at completion of study period II (Week 48).

Originally, this study was planned to be analyzed at least 3 times, at completion of study period I (Week 12), at completion of study period II (Week 48), and at the final analysis after all patients complete the study in the protocol.

No second analysis is required as primary analysis (first analysis) contains data through Week 48.

Changes to the protocol

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

- Section 2.2, Section 4.1, Section 4.3, Section 6.1.5: revised to update the duration of the optional extension period and end of study definition and to exclude the long term safety follow-up study modalities.
- Section 7.1.4.1: the definition of Withdrawal of Consent has been updated in line with the latest Novartis protocol template updated following the release of the General Data Protection Requirements (GDPR) in the European Economic Area (EEA).
- Section 10: removed the description of second analysis at completion of study period II (Week 48).

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

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

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

[redacted]

Summary of previous amendments

Amendment 3 (07-Aug-2017)

Amendment rationale

Study status: As of 14 Jul 2017, 6 patients have been enrolled into the study and received study drug.

The main purpose of this amendment is to clarify the duration of the optional extension period in order to collect long-term safety and efficacy data as well as to provide continued access to the study drug for those patients benefitting from the treatment until a separate long-term safety follow-up study is set up at participating sites. Based on this extension, the end of study definition has been updated. In addition, the long-term safety follow-up study modalities have been detailed.

Other protocol changes include:

- In view of the results of the thorough QT study CLCI699C2105, which showed that the increase in QTcF caused by osilodrostat at therapeutic doses is below the threshold of regulatory concern, the QT-specific concomitant medication guidance for osilodrostat was revised to limit the list of prohibited drugs to medications with a "Known risk to cause TdP" and "Possible risk to cause TdP", instead of all drugs known to prolong QT. This change is also in alignment with the terminology used in the QT Drug Lists (CredibleMeds®).
- The risks section was updated to include neutropenia, which is a known effect related to the decrease of cortisol in patients with Cushing's disease, in line with cases observed in clinical trials with osilodrostat.

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.

- Protocol synopsis: edited to be consistent with the changes made throughout the protocol.
- Section 2.2, Section 4.1, Section 4.3, Section 6.1.5: revised to update the duration of the optional extension period and end of study definition and to include the long term safety follow-up study modalities.
- Section 2.6: updated to include the possibility of neutropenia based on observed cases with LCI699
- Table 3-1, definition of the partial responder has been updated to be consistent throughout the protocol.
- Section 6.4.2, Section 6.4.2.1, Appendix 3: revised to update the QT-specific concomitant medication guidance for LCI699 limiting the list of prohibited drugs to medications with a "Known risk to cause TdP" and "Possible risk to cause TdP" instead of all drugs known to prolong QT
- Figure 7-2: added QT Monitoring Flow Chart
- Section 7.2.1: added to collect 24-hour UFC as required by investigators.

[redacted]

- Section 7.2.3: revised to clarify the serial PK sampling if osilodrostat administration was interrupted prior to a planned visit.
- Section 13: Reference added.

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

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

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

Amendment 2 (11-Nov-2016)

Amendment rationale

Study status: As of 3 October 2016, 2 patients have been enrolled into the study and received study drug

The primary purpose of this protocol amendment is to facilitate enrollment by amending some of the inclusion/exclusion criteria based on feedback from the study investigators.

This amendment included the following changes:

1. Inclusion criterion #1: Change upper limit age from 75 years old to 85 years old
2. Inclusion criterion #2: Remove mandatory wash-out of steroidogenesis inhibitors before mean Urine Free Cortisol (mUFC) evaluation at screening (**See Inclusion criterion #4a for the steroidogenesis inhibitors**)
3. Exclusion criterion #3: Allow patients who have an inherited syndrome causing hypercortisolism

The rationale for these changes are presented below:

Inclusion criterion #1: Include Male or female patients aged 18 - 85 years (Change upper limit age from 75 years old to 85 years old)

There is the potential for a decrease in liver/renal/heart function or an increase in underlying disease with advancing age. However these patients are excluded by the following exclusion criteria. Therefore the patients' safety is considered to be adequate even if the age ceiling is increased from 75 years old to 85 years old

- Patients with insufficient liver/renal/heart function are excluded (exclusion criteria 6, 8, 9 and 10).
- Patients who have underlying disease that can interfere with the conduct or evaluation of study is also excluded (exclusion criteria 7 and 15).

[redacted]

Inclusion criterion #2: 24-hour urine samples can be collected during screening without washout of steroidogenesis inhibitors to confirm mUFC > 1.3 x ULN (See Inclusion criterion #4a for the steroidogenesis inhibitors)

In this amendment, 24-hour urine samples can be collected during screening without washout of steroidogenesis inhibitors to confirm mUFC > 1.3 x ULN. However, washout before baseline laboratory evaluation will remain mandatory so that reference values for mUFC and other parameters at pre-dose will be collected to evaluate efficacy assessment.

At screening, confirmation of mUFC > 1.3 x ULN with or without washout increases patient convenience and avoids unnecessary exposure to elevated cortisol levels since patients who meet the mUFC inclusion criteria without washout will also be required to meet mUFC criteria with washout, thus confirming the diagnosis of Cushing's syndrome.

In the case of patients who do not meet the mUFC criteria without washout, rescreening after washout is recommended to eliminate the possibility of inappropriate screen failure.

Exclusion criterion #3: Include patients who have an inherited syndrome causing hypercortisolism:

Previously, the rare inherited syndromes causing hormone over secretion (i.e. Carney Complex, McCune-Albright syndrome, Multiple endocrine neoplasia-type 1 [MEN-1], and aryl hydrocarbon receptor interacting protein [AIP]) were excluded to limit the heterogeneity of the study population.

In this amendment, these patients will be included because the target population of C1201 study is already a heterogeneous population of various types of Cushing's syndrome [i.e. ectopic corticotropin syndrome, adrenal adenoma, adrenal carcinoma, ACTH-Independent Macronodular Adrenal Hyperplasia (AIMAH), or Primary Pigmented Nodular Adrenal Dysplasia (PPNAD)] from the beginning of study. In fact, most cases of PPNAD occur in patients with the inherited syndrome Carney Complex.

The inclusion of patients with the inherited syndromes may impact the study population in the following ways: on the one hand, heterogeneity will increase, thereby requiring additional caution in interpreting the results; on the other hand, this amendment would reflect more broadly the natural heterogeneity of Cushing's syndrome as it presents in clinical practice.

Other protocol changes are:

- To provide more information regarding the study drug, the results of the thorough QT/QTc study (CLCI699C2105) of osilodrostat in healthy volunteers has been added.
- To reduce the risk of overdosing error, the 20 mg tablet strength will no longer be available for use in this study.
- To distinguish between recommended and mandatory dose interruptions or reduction, language has been added for clarification.
- Inclusion of updated and more conservative hepatic safety-related discontinuation criteria.

The duration of the optional extension period is increased in order to collect additional long-term safety data as well as to provide continued access to the study drug for those patients benefitting from the treatment. The reason for collecting a long term safety data is valuable because the drug is intended to be used as a long term treatment in these patients. The reason

[redacted]

for collecting a long term data is not because of the new safety reasons. The optional extension period will end when seamless transition to a long-term safety follow-up study is possible or osilodrostat is commercially available, whichever is earlier. In the first case, patients who continue to benefit from the treatment will be offered participation in the separate long-term safety follow-up study.

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 font for insertions.

- Protocol Summary: Changes in the main body of the protocol are also implemented in the relevant sections of the protocol synopsis.
- Section 1.2.1, 6.1 and 6.6: Added a description that the 20 mg tablet strength will no longer be used.
- Section 1.2.1.2.4: Added the cardiac repolarization (QT/QTc) data of osilodrostat in healthy volunteers.
- Section 2.2, 4.1, 4.3, 6.1.5, 7.1, 7.1.3, Table 7-1, 7-2 and 7-3: Updated to include the changes due to the increase in duration of the optional extension period and the study period.
- Section 5.1: Provided explanation about adjustment of target patient number based on enrollment status.
- Section 5.2:
  - Inclusion criterion #1: Changed upper limit of age from 75 to 85 years old.
  - Inclusion criterion #2: Changed wash-out of steroidogenesis inhibitors to not mandatory before mUFC evaluation at screening.
- Section 5.3:
  - Exclusion criterion #3: Changed to allow patients who have a known inherited syndrome.
- Section 6.1.1: Added a description of guidance on dose adjustments.
- Section 6.3.1, Table 6-1 and Table 6-2: Clearly distinguished between recommended and mandatory dose interruptions and/or dose reduction.
- Table 6-2: Updated discontinuation criteria for patients with AST or ALT > 10.0 x ULN.
- Table 7-3: Added visit schedule for the optional extension period of more than one year.
- [redacted]
- Section 7.1.4: Added hepatic safety-related discontinuation criteria.
- Section 8.1.3: Added definition of adverse events of special interest.
- Section 8.1.3.1: Added results of the thorough QT/QTc study (CLCI699C2105) data of osilodrostat in healthy volunteers and removed preliminary clinical data.
- Section 10 and 10.8: Provided explanation of certain parts of data analysis.
- Appendix 2: Updated to remove the corticosteroids (budesonide, fluticasone) as use of glucocorticoids is prohibited except under certain conditions as specified in Section 6.4.2.

[redacted]

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

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

Amendment 1 (29-Feb-2016)

Amendment rationale

The primary purpose of this protocol amendment is to improve patient safety by adding specific criteria for the identification and management of patients with potential drug-induced liver injury (DILI). Although there are no known cases of suspected DILI in patients treated with osilodrostat to date, these criteria are added in the event that a case of suspected DILI arises in the future.

Additional changes include;

- Addition of the benefit-risk assessment of osilodrostat
- Clarification of the correct procedures for dose adjustment and drug dispensation to emphasize the education of sites and patients

[redacted]

- Implementation of partial pressure of carbon dioxide (pCO_2) is added as an alternative lab assessment to bicarbonate for evaluation of acid-base status at study sites that are not able to measure bicarbonate directly.

In addition, editorial changes and clarifications were made at various places in the protocol.

As of 30 October 2015, 2 patients have provided written informed consent for the study and 1 patient has received osilodrostat.

Changes to the protocol

Section 2.6: Addition of the benefit-risk assessment of osilodrostat

Section 5.3 Item 10: Implement the new criteria for exclusion of patients with liver disease

Section 6.3.1: Implement the dose modification criteria for abnormal liver function.

Section 6.3.2.1: Implement the follow up procedure for potential drug-induced liver injury cases

Section 6.1, Figure 6-1, Section 6.6, Table 6-3: Clarification of the correct procedures for dose adjustment and drug dispensation

Section 7.2.2.4.2, Table 7-5: Implement pCO_2 as an alternative option of bicarbonate

[redacted]

Section 8.2.2: Updated to introduce new protocol template

[redacted]

Section 10.5.3.3: Add analysis plan of laboratory test for liver function.

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

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

[redacted]

Protocol summary:

Title	A Phase II, open-label, dose titration, multi-center study to assess the safety/tolerability and efficacy of osilodrostat in patients with all types of endogenous Cushing's syndrome except Cushing's disease
Brief title	Study of efficacy and safety osilodrostat in Cushing's syndrome.
Sponsor and Clinical Phase	Novartis, phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to investigate the efficacy and safety of osilodrostat in patients with Cushing's syndrome (CS) due to causes other than Cushing's disease (CD) in Japan. In Japan, the proportion of patients with CD in the population of CS patients is lower compared to Western countries. In Western countries, the proportion of CS patients with CD is around 70%, while in Japan, the proportion of CS patients with CD is approximately 35%. Therefore, the development of osilodrostat for the population of patients with CD only will not satisfy the medical needs of all patients with endogenous CS in Japan.
Primary Objective(s) and Key Secondary Objective	To assess the percent change from baseline in the mean Urine Free Cortisol (mUFC) at the individual patient level at Week 12
Secondary Objectives	To assess the percent change from baseline in the mean urine free cortisol (mUFC) at the individual patient level at Week 24 and Week 48 To assess the absolute and percent change from baseline in mUFC at Week 12, Week 24 and Week 48 To assess the complete, partial, and overall response rate at Week 12, Week 24 and Week 48 To assess the absolute and percent change from baseline in morning serum cortisol at the individual patient level at Week 12, Week 24 and Week 48 To assess the absolute and percent change from baseline in morning serum cortisol at Week 12, Week 24 and Week 48 To assess the absolute and percent change from baseline in steroid hormones at the individual patient level at Week 12, Week 24 and Week 48 To assess the change from baseline in cardiovascular-related metabolic parameters associated with CS at Week 12, Week 24 and Week 48 To assess the general safety of osilodrostat To assess the change from baseline in Patient-Reported Outcome (Health Related Quality of Life) at Week 12, Week 24 and Week 48 To evaluate PK of osilodrostat in patients with CS
Study design	This is a phase II, single arm, open-label, dose titration, multi-center study consisting of two distinct study periods (12 weeks and 36 weeks) plus an optional extension period.
Population	The patient aged 18 - 85 years, non-CD patients with CS who have persistent or recurrent hypercortisolism after primary surgery and/or irradiation and/or chemotherapy, and patients *de novo* CS who are not surgical candidates for medical reasons, or refuse to undergo surgery.
Inclusion criteria	● Patients must have confirmed CS [i.e. ectopic corticotropin syndrome, adrenal adenoma, adrenal carcinoma, ACTH-Independent Macronodular Adrenal Hyperplasia (AIMAH), or Primary Pigmented Nodular Adrenal Dysplasia (PPNAD)]. ● Patients are expected to remain in stable condition for at least 5 months. ● For patients on medical treatment for hypercortisolism due to CS the washout periods must be completed prior to baseline efficacy assessments.

[redacted]

Exclusion criteria	● Patients with Cushing's disease ● History of hypersensitivity to osilodrostat or to drugs of similar chemical classes ● History of malignancy of any organ system [with the exception of: a) malignancy causing ectopic corticotropin syndrome, or b) localized basal cell carcinoma of the skin], treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases ● Patients receiving treatment for malignancy (e.g., cytotoxic chemotherapy, molecular targeting drugs, somatostatin analogue) within 4 weeks or ≤ 5 x half-life of the agent (whichever is longer) before first dose of osilodrostat ● Patients with risk factors for QTc prolongation or Torsades de Pointes
Investigational and reference therapy	Osilodrostat (LCI699) at 2 mg b.i.d., 5 mg b.i.d., 10 mg b.i.d., 20 mg b.i.d. and 30 mg b.i.d.
Efficacy assessments	● 24-hour urine to test for Urine Free Cortisol and creatinine
Safety assessments	● Adverse events ● Laboratory evaluations (biochemistry, hematology, coagulation, thyroid panel, fasting glucose, urinalysis and pregnancy test) ● ECG, vital signs and physical exam
Other assessments	● PK evaluation [redacted]
Data analysis	The primary objective is to assess the percent change from baseline in the mean Urine Free Cortisol (mUFC) in individual patient level data at week 12. The primary endpoint defined as the patients level percent change from baseline in mUFC will be listed. No statistical analysis including descriptive summary will be performed for the primary analysis. The assessment of the efficacy will be based on the review of individual patient listing and figures due to very small sample size and expected variability in response caused by various patient background and disease. Therefore, no statistical hypothesis is set up for this study.
Key words	Cushing's syndrome, osilodrostat, LCI699, ectopic corticotropin syndrome, adrenal adenoma, adrenal carcinoma, AIMAH, PPNAD

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

1.1.1 Epidemiology and pathogenesis of Cushing's syndrome (CS)

Cushing's syndrome (CS) is rare: the reported incidence of either endogenous CS or Cushing's disease (CD) in the U.S., European countries (Spain, Denmark, Belgium, and Iceland) and New Zealand has been estimated to be 1.2 to 2.4 cases per million persons per year (Etxabe and Vazquez 1994, Lindholm et al. 2001, Daly et al. 2006, Arnardottir and Sigurjonsdottir 2011, and Bolland et al. 2011). The endogenous CS is classified into Adrenocorticotropic hormone (ACTH)-dependent and ACTH-independent etiologies based on cause of disease. The most of CS is ACTH-dependent in the U.S. and European countries, and the most common cause of ACTH-dependent CS is CD which occurs is due to an ACTH-secreting pituitary corticotroph adenoma. The other main cause of ACTH-dependent CS is ectopic ACTH secretion from non-pituitary tumors (e.g., small cell lung cancer). The ACTH-independent etiologies of CS are adrenal diseases such as adrenal tumors (adenomas or carcinomas) or bilateral adrenal hyperplasia. In U.S., the reported incidence of CD was 70% of CS. The incidences of ectopic corticotropin syndrome and cortisol-secreting adenoma were 12% and 18% of CS, respectively (Porterfield et al. 2008).

In Japan, Ministry of Health, Labour and Welfare working group has conducted a survey in 1997 and the prevalence of CS was estimated as 1250 cases. In the 417 cases of CS which were actually reported, 35.8% had CD, 47.1% had adrenal adenoma, 17.1% had other cause of CS (Nawada et al. 1999).

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 (Etxabe and Vazquez 1994 and Arnaldi et al. 2003). The increased cardiovascular risk is related to the following clinical manifestations of CS: metabolic syndrome, insulin resistance, visceral obesity, glucose intolerance, hypertension, dyslipidemia, and hypercoagulation. Other clinical signs and symptoms of CS include: supraclavicular and dorsal fat pads; proximal muscle weakness; osteoporosis with increased risk of fractures; skin changes (wide purple striae, hirsutism, acne); impaired immune function with increased risk of infection; neuropsychiatric disorders (depression, mood changes, and cognitive impairment), hypogonadism, and menstrual disorders in women (Newell-Price et al. 2006).

1.1.2 Current treatment modalities

For any types of CS the first line therapeutic option is surgical resection. However, patient may be treated with medical therapy during the pre-surgery period to control the hypercortisolism. The recurrence of CD after the surgical resection of the pituitary tumor is reported to be more than 20%. Radiation therapy at pituitary gland is used as an option to those who have recurred CD after surgery but the remission rate is less than 50% and takes long time to gain the effect. The surgery is a primary option for patients with the adrenal adenoma in principle but the drug therapy is used to patients who are not eligible for the surgery. Surgical resection of the cancer

[redacted]

or chemotherapy is used for the treatment of ectopic ACTH producing tumor. If the surgery is not applicable, the drug therapy for the hypercortisolemia or a bilateral adrenal resection is applied. For ACTH-independent macronodular adrenal hyperplasia (AIMAH) and primary pigmented nodular adrenal dysplasia (PPNAD) which causes the hyperplasia of bilateral adrenal, the bilateral adrenal resection is used as the curative therapy but depending on the disease condition, subtotal resection is applied. The drug therapy is applied as a part of the preoperative procedure or for those who are not eligible for the surgery. There's no major difference in the treatment option between Japan and US/EU.

In Japan, mitotane, trilostane, and metyrapone are approved for CS. Mitotane has the cytotoxic effect which induces the adrenal cortex cytotoxicity and the inhibitory effect on the steroid synthase. The occurrence rate of adverse event (AE) by mitotane is 80% and the gastrointestinal manifestation, the central nerve manifestation, and adrenal failure are reported as common AEs. Trilostane inhibits the 3β-hydroxysteroid dehydrogenase and inhibits the synthesis of cortisol and aldosterone. Nausea, vomiting, liver deficiency, and rash are reported as the side effect. Metyrapone has the inhibitory effect on 11β-hydroxylase and inhibits the synthesis of cortisol and aldosterone. Metyrapone was approved for CS by the public domain submission under the scheme by "the committee for the unapproved/off-label drug with the high unmet medical needs" in Japan. As the safety profile of metyrapone is milder than the mitotane profile, and the inhibitory effect of cortisol synthesis is stronger compared to the effect of trilostane, metyrapone is used widely in Japan for the treatment of CS. However, there are patients who have suboptimal effect with Metyrapone, the proportion of patients not adequately controlled is in the range of 20 - 40% (Feelders et al. 2010, Valassi et al. 2012), In addition, there is a drug compliance issue due to the need of drug administration 1-4 times per day.

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

1.2.1 Overview of osilodrostat (LCI699)

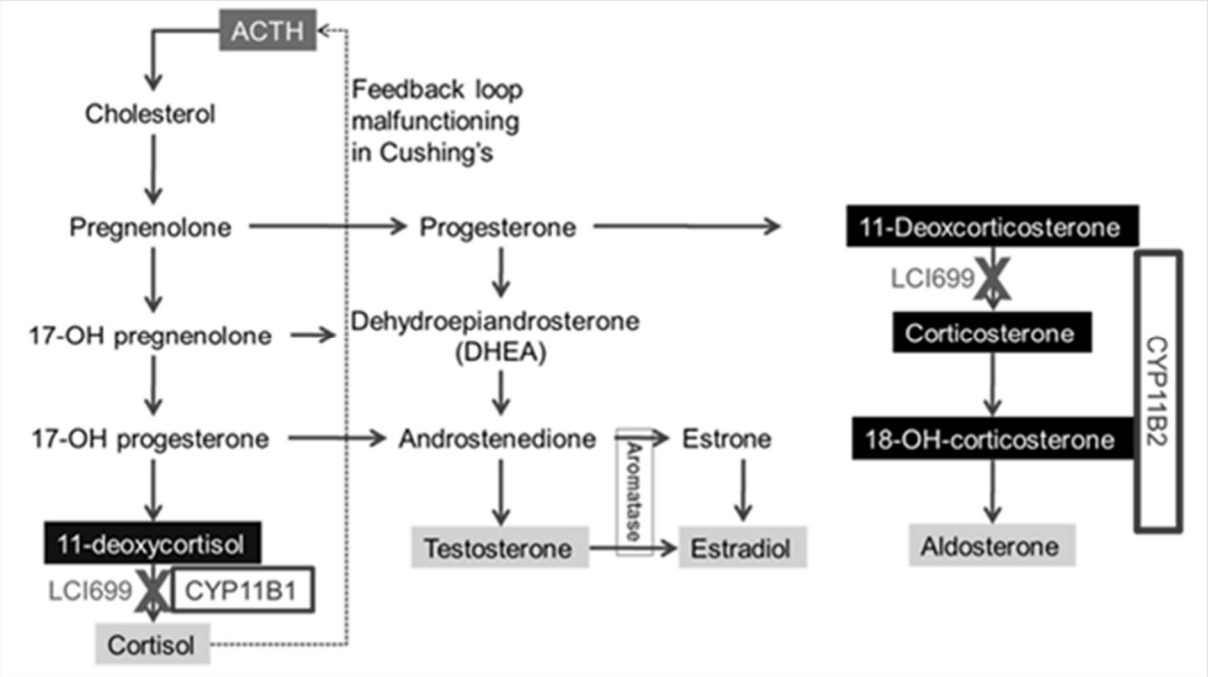
Osilodrostat is a new chemical entity with the chemical structure 4-[(5R)-6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-5-yl]-3-fluorobenzonitrile phosphate.

Osilodrostat 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. This drug also inhibits aldosterone synthase (CYP11B2), and therefore is a dual inhibitor of both cortisol and aldosterone synthesis. It is manufactured as a phosphate salt and available in film-coated tablets of 1 mg, 5 mg, 10 mg and 20 mg for this phase II study: On 22 Aug 2016 (before Amendment #2), the 20 mg tablet strength was discontinued for use in the trial, in order to reduce the risk of dosing error in which the patient took more than the prescribed dose. Remaining supplies of the 20 mg tablets were to be collected from the sites.

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

[redacted]

Figure 1-1 Mechanism of action of osilodrostat (LCI699) in Cushing's disease



1.2.1.1 Non-clinical experience

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

1.2.1.1.1 Non-clinical pharmacology

The oral absorption of *In vivo* osilodrostat in rat and dog was rapid with complete bioavailability indicating a minimal first-pass effect. The plasma half-life of osilodrostat in rat and dog was short (~ 2 h). Exposure was dose-proportional within the dose range investigated in the rat but over-proportional in dogs and mice. No accumulation or gender differences were observed in either species. Protein binding of osilodrostat in animals and humans was low (26.6-36.4%). osilodrostat rapidly and extensively distributed to rat tissues. The highest tissue-to-blood ratios (≥ 9) were observed in the uveal tract, skin, eye, glandular stomach, small intestine, liver, and adrenal cortex. Drug-related radioactivity showed a significant affinity to melanin in the skin and uveal tract. Drug-related radioactivity showed a moderate distribution to brain, spinal cord and the testis with tissue-to-blood concentration ratio of 0.73-1.7. The elimination of osilodrostat is mainly through metabolism and excretion in urine (~79% in rats and ~90% in dogs; unchanged osilodrostat ~ 5-10% in urine and < 3% in feces). Based on *in vitro* CYP P450 inhibition profile and predicted steady state maximum concentration of 1.54 µM at 30 mg twice daily in humans, there is potential of drug- drug interaction for osilodrostat. Results from a clinical drug-drug interaction study are summarized in Section 1.2.1.2.1. It is unlikely for osilodrostat to increase in the systemic exposure of co-medications whose clearance is mediated by P-gp, BCRP, OAT1, OAT3, OCT1, and OCT2 transport activity.

[redacted]

1.2.1.1.2 Preclinical safety

Safety pharmacology:

In safety pharmacology studies, proarrhythmic indices and QTc interval prolongation were observed in *in vitro* study in isolated rabbit heart and *in vivo* studies in dog and monkey with osilodrostat. Proarrhythmic indices were observed at 10 μM in isolated rabbit heart assay. QTc interval prolongation was noted at 50 mg/kg after 2 weeks of intravenous dosing in dogs, at 30 mg/kg oral (gavage) after single dose, and at 10 mg/kg/day in a two week study in monkeys.

Toxicology:

No acute toxicity was observed in mice following administration of oral doses up to 125 mg/kg. In repeated dose general toxicity studies up to 26-weeks in duration in the rat, and up to 39-weeks in the dog, the main target organs were central nervous system (CNS), liver, female reproductive organs, and adrenal gland. Reversible CNS effects were seen at very high doses in dogs (≥ 10 mg/kg) and mice (doses ≥ 30 mg/kg). Hepatocellular hypertrophy and vacuolation were seen in 13-week and 26-week rat studies at doses ≥ 5 mg/kg and in a 13-week study in mice at doses ≥ 10 mg/kg (partially reversible). In female dogs, transient increases in ALT and AST were observed at week 5 during the 13-week study at 0.1 and 10 mg/kg. Effects on female reproductive organs (ovary, uterus and vagina) were seen in rats at doses ≥ 5 mg/kg (reversible) and in mice at doses ≥ 30 mg/kg. Male reproductive organ changes were limited to a decrease in prostate weights (no microscopic correlate) in the 26-week rat study at 20 mg/kg. No effects on female or male reproductive organs were found in dogs. In the adrenal cortex, morphological alterations were observed in dogs (zona glomerulosa) and at much higher exposure in rats (zona fasciculata/glomerulosa). They may be a result of the inhibition of adrenocortical steroid biosynthesis leading to an adaptive induction of the aldosterone/cortisol synthase pathway. In the chronic toxicity studies, the NOAEL was 2 mg/kg in the rat (26-week), and was 10 mg/kg in the dog (39-week).

In genetic toxicology studies, no evidence of mutagenic activity was observed in the Ames test, and no evidence of chromosomal damage in the *in vitro* micronucleus test. Clastogenic effects at high concentrations with and without metabolic activation were reported in cultured human peripheral blood lymphocytes. *In vivo* genotoxicity tests in rats (micronucleus test and comet assay) were clearly negative and it is therefore concluded that osilodrostat has no relevant genotoxic potential in humans.

In reprotoxicity studies (embryo fatal developmental study in rats and rabbits, fertility and early development study in rats), embryo/fetal toxicity was observed at doses that produced maternal toxicity in the rat and the rabbit, and increased incidence of fetal malformation was observed in rats (only occurred at the maternally toxic dose).

1.2.1.2 Clinical experience

1.2.1.2.1 Clinical pharmacokinetics

The pharmacokinetics of osilodrostat has been studied in healthy volunteers, patients with hypertension, and patients with hyperaldosteronism, as well as in an ongoing proof-of-concept study in CD patients. For detailed information, please refer to the [Investigator's Brochure].

[redacted]

Following single oral doses of 0.5 mg to 200 mg to healthy volunteers under fasting conditions, osilodrostat was rapidly absorbed with a Tmax of approximately 1 hour. The elimination half-life of osilodrostat was 3-5 hours across all doses examined. The pharmacokinetics of osilodrostat were over-dose proportional in the dose range of 0.5 to 200 mg (single dose); for a 2-fold increase in dose, the AUC increase would be about 2.4-fold, and Cmax increase would be 2.1-to 2.4-fold [CLCI699A2101]. Metabolism was the major clearance pathway for osilodrostat in humans with renal clearance making only a minor contribution. Metabolism of osilodrostat was extensive in humans via multiple pathways (and combination of pathways) [CLCI699C2101]. Results from a cocktail drug-drug interaction study [CLCI699C2102] showed that osilodrostat is a weak inhibitor for CYP3A4/5 and CYP2D6 (increased AUCs of midazolam and dextromethorphan ~1.5-fold), and a moderate inhibitor for CYP1A2 and CYP2C19 (increased AUC of caffeine and omeprazole ~2.5- and ~1.9-fold, respectively).

Impact of ethnic origin on osilodrostat pharmacokinetics was investigated in Caucasian and Japanese healthy male subjects following single and multiple doses of osilodrostat (0.25, 0.5, 1, 2 mg). Osilodrostat exposure (AUC) was 18%, 44%, and 66% higher in Japanese healthy volunteers in comparison to Caucasians after single dose of 0.5 mg, 1 mg and 2 mg osilodrostat. Body weight difference (mean body weight: 64.6 to 68.6 kg for Japanese vs. 70.7 to 77.6 kg for Caucasians) was not shown to be a major determinant of the race effect on exposure [CLCI699A2102].

1.2.1.2.2 Results of CLCI699C2201 study in Cushing's disease

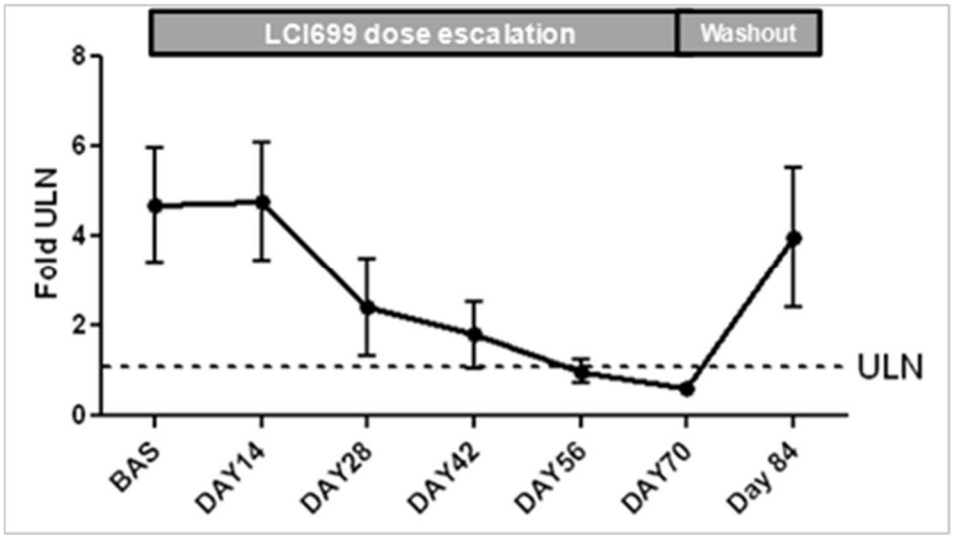
The purpose of the CLCI699C2201 study was to determine whether the ability of osilodrostat to inhibit 11β-hydroxylase could safely reduce urinary free cortisol (UFC) in patients with CD. This was initially studied over a 10-week treatment duration Proof-of Concept (Part I). Part II of the study aimed 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 for a total duration of 22 weeks.

In Part I, osilodrostat was effective in controlling cortisol production in all 12 patients studied. At daily osilodrostat doses between 2 mg b.i.d. and 50 mg b.i.d., 24-hour mean UFC (mUFC) decreased rapidly and normalized at least once in all patients studied. In general at 5 mg b.i.d. patients showed mUFC reduction after 2 weeks (at first mUFC measurement after dose titration).

The primary endpoint, defined as mUFC ≤ 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 (± SD) of osilodrostat required to reach the primary endpoint was 13.5 ± 13.9 mg b.i.d. with 75% of patients normalizing mUFC on ≤ 10 mg b.i.d. At Day 84, two weeks after osilodrostat was withdrawn, mUFC levels increased to a mean of 4-fold above upper limit of normal (ULN) (Figure 1-2).

[redacted]

Figure 1-2 Arithmetic mean and SE plots for fold ULN of mUFC (PD analysis set)

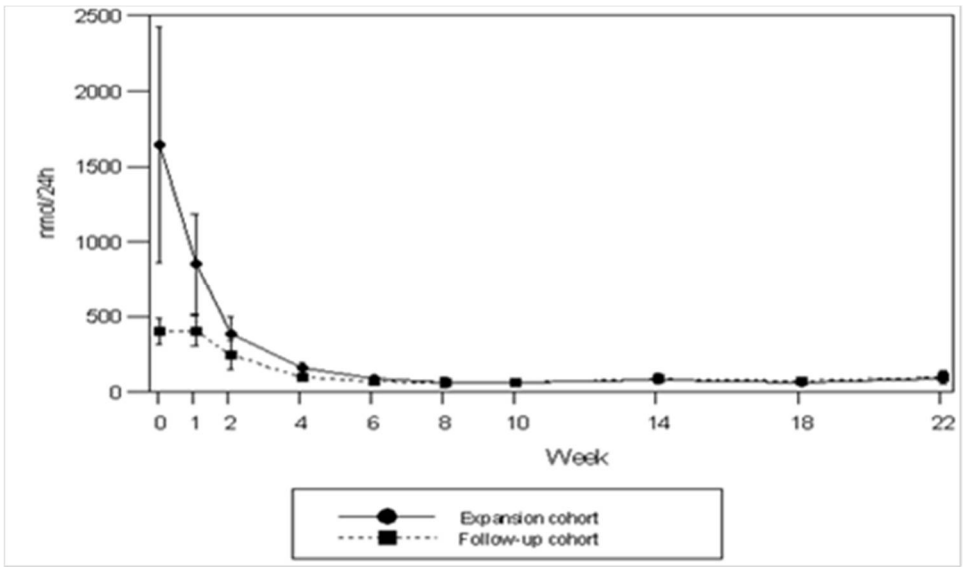


Source: In-text Figure 11-2, 10-week interim CSR study [CLCI699C2201]

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.

In Part II, 17 out of 19 patients completed the 22 weeks treatment period and 15 had normal mUFC levels at week 22 (79%). During treatment with osilodrostat, the mean mUFC levels decreased quickly and stabilized to a normal level (11 to 138 nmol/24h) at Week 4 (Figure 1-3). After Week 4, normal mean mUFC 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.

Figure 1-3 Mean (+/-SE) mUFC (nmol/24h) over time by cohort



Source: In-text Figure 11-1, 22-week interim CSR study [CLCI699C2201]

[redacted]

1.2.1.2.3 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. AEs were generally of mild to moderate intensity. Both 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.

In Part I of CLCI699C2201 study, all 12 patients (100%) experienced adverse events but these were generally mild to moderate in severity (NCI CTC grade 1 or grade 2). 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 II, osilodrostat was generally well tolerated. Except for one patient in the expansion cohort, all patients experienced AEs, grade 1/2 in most of the cases. Adrenal insufficiency, nausea, fatigue and increased levels of oxycorticosteroids, blood corticotrophin, blood testosterone in females were the most common AEs suspected to be drug related (by preferred term).

Two patients experienced a total of 3 SAEs.

One patient experienced grade 3 pituitary-dependent CS (preferred term). The SAE resulted in hospitalization/prolonged hospitalization and was not suspected to be related to the study drug. This SAE was continuing at the time of the data cut-off date.

Another patient experienced 2 SAEs concurrently: grade 3 gastroenteritis (preferred term) and grade 1 Electrocardiogram QT prolongation (preferred term). The gastroenteritis resulted in hospitalization/prolonged hospitalization, was not suspected to be related to the study drug and resolved with concomitant medication. The Electrocardiogram QT prolongation was suspected to be related to the study drug by the investigator, but causality is not clear. There were no cardiac symptoms or arrhythmia reported. The SAE “electrocardiogram QT prolongation” was ongoing at the time of the data cut-off date.

One patient discontinued the study drug due to AEs. This patient reported (by preferred term) grade 3 papule, and grade 1 diarrhea, malaise, muscular weakness and nausea. All the AEs were suspected to be related to study drug and the patient discontinued the study drug after two weeks treatment

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

[redacted]

- 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, and more pronounced in women than in men)

A more detailed list of potential AEs related to the mechanism of action of osilodrostat can be found in Section 8.1.3 Adverse events of special interest. For a comprehensive review of clinical safety data with osilodrostat, see the [Investigator's Brochure].

1.2.1.2.4 Study CLCI699C2105: QT/QTc data in healthy volunteers

For detailed information, please refer to the [Investigator's Brochure].

The cardiac repolarization liability of osilodrostat was assessed in the definitive ICH E14 compliant thorough QT/ QTc Study (TQT) study [CLCI699C2105] in 86 healthy male and female subjects.

The final results showed that the predicted mean QT effect of osilodrostat was below the threshold of regulatory concern (i.e., an upper boundary of the 90% CI < 10 ms) and fully support the use of osilodrostat doses up to 30 mg.

2 Rationale

2.1 Study rationale and purpose

Osilodrostat is a potent inhibitor of 11β-hydroxylase, 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.

The effect of osilodrostat in patients with CD and recurrent or persistent hypercortisolism, was investigated in the Proof-of-Concept (PoC) study [CLCI699C2201] and demonstrated a response rate of 100% after 10 weeks, and approximately 80% after a new treatment period of 22 weeks of osilodrostat treatment.

A Phase III study [CLCI699C2301], intended to support the registration of osilodrostat for the treatment of patients with CD is ongoing.

In Japan, the proportion of patients with CD in the population of CS patients is lower compared to Western countries. In Western countries, the proportion of CS patients with CD is around 70%, while in Japan, the proportion of CS patients with CD is approximately 35%. Therefore, the development of osilodrostat for the population of patients with CD only will not satisfy the medical needs of all patients with endogenous CS in Japan. Hence, it is necessary to investigate the efficacy and safety of osilodrostat in patients with CS due to causes other than CD in Japan.

2.2 Rationale for the study design

This is a Phase II, single arm, open-label, dose titration, multi-center study consisting of two distinct study periods plus an optional extension period with non-CD patients with CS.

Three periods are Study period I, Study period II and Optional extension period. Study period I (12-weeks duration) is a dose titration period to achieve individual stable therapeutic dose and to assess the efficacy and safety. Individual dose titration is required based on the available data due to high inter-subject variability in effective dose and narrow therapeutic window (risk of hypocortisolism-related adverse events including acute adrenal insufficiency). Study period II (36-weeks duration) is to assess the sustainability of efficacy and to assess the long term safety for the patients who tolerate and agree to continue the study treatment and the aim of the optional extension period is the same as Study period II for the patients who are willing to enter this period. The optional extension period will end after all patients have completed Week 72 or discontinued early (prior to Week 72). The patient can either be offered a local alternative treatment option or stay in the study until the study end (9 months after the last patient completes Week 72)

Based on the very small sample size and expected variability in response caused by various patient background and disease, the primary analysis will report the individual patient data.

2.3 Rationale for dose and regimen selection

The rationale for b.i.d. dosing of osilodrostat is based on its half-life of 3-5 h. This regimen was used in the PoC study [CLCI699C2201] as well. Originally modeling of PK exposure estimated that a dose of 4-5 mg b.i.d. is expected to achieve a plasma concentration above the *in vitro* IC50 for CYP11B1 (2.5 nM) for a full 24 hours for efficacy consideration; however, 2 mg b.i.d was chosen to be the starting dose in the PoC study based on safety considerations, i.e., to reduce the risks associated with potential hypocortisolism-related adverse events:

- Glucocorticoid withdrawal due to rapid correction of elevated serum cortisol
- Biochemical hypocortisolism [UFC < Lower limit of normal (LLN)]
- Symptomatic hypocortisolism or adrenal insufficiency (potentially life-threatening)

There were four events of suspected hypocortisolism (glucocorticoid withdrawal) that improved with dose reduction or dose interruption during the 10-week PoC study [CLCI699C2201]. Since these events occurred during the 10-week dose titration period, they support a conservative approach to the starting dose of osilodrostat. In addition, since the 10-week analysis, 2 patients in the ongoing study [CLCI699C2201] had adrenal insufficiency on 2 mg b.i.d., and their osilodrostat dose was reduced to 1 mg b.i.d..

The 10-week analysis of the PoC study [CLCI699C2201] showed that the dose of osilodrostat required the normalization of mUFC ranged from 2 mg b.i.d. to 50 mg b.i.d. after individual dose titration, with nearly all patients (11/12) achieving UFC normalization at > 2 mg b.i.d. Trough concentrations at mUFC normalization also varied widely, ranging from 0.3-49 ng/mL. This indicates that there is a broad range (up to 25-fold in osilodrostat dose) of between-patient sensitivity to osilodrostat with respect to normalization of mUFC, and there was no apparent relationship between the therapeutic dose or exposure (trough concentrations) and the baseline mUFC.

Thus, it appears that individual dose titration starting at 2 mg b.i.d. is appropriate to assess the efficacy and safety of osilodrostat. Fixed-dose comparisons of osilodrostat doses would carry the risk of hypocortisolism if a relatively high dose is administered to a patient who is very

[redacted]

sensitive to osilodrostat; in extreme cases, such a complication could present as a potentially life-threatening adrenal crisis.

This study will therefore start with individual patient dose titration period during the first 12 weeks with the following dose escalation sequence 2 mg b.i.d., 5 mg b.i.d., 10 mg b.i.d., 20 mg b.i.d., and 30 mg b.i.d.. The dose of osilodrostat is titrated on the basis of the serum cortisol levels that are collected every week for initial 4 weeks, up to maximum dose of 10 mg b.i.d.. Thereafter, the dose can be further increased, if needed, at 2-week intervals in the dose titration period. In CLCI699C2201, mUFC was used for dose titration. In this study, serum cortisol will be used since patients with causes of endogenous CS other than CD are expected to have persistently elevated serum cortisol levels, without a daily circadian rhythm. In addition the turnaround time of serum cortisol is expected to be shorter than UFC. Based on the 2 patients (see above) in the ongoing study [CLCI699C2201] who had adrenal insufficiency on 2 mg b.i.d., the dose can be lowered to 1 mg b.i.d. if this occurs in the present study. Further dose reductions to 1 mg once daily must be discussed with the sponsor before implementation.

Please refer to Section 6.1.1 for more detailed information regarding dose adjustment.

2.4 Rationale for choice of combination drugs

Not applicable

2.5 Rationale for choice of comparators drugs

Not applicable

2.6 Benefit-Risk Assessment of osilodrostat in study population

Appropriate eligibility criteria, as well as specific dose modification and stopping rules, are included in this protocol. Recommended guidelines for supportive management of study-drug induced adverse events are provided in Section 6.3.1.

Potential patient benefits

There is an unmet medical need in CS patients which is a rare and serious disease with limited options for medical therapy. Phase II data demonstrated normalization of mean UFC in 11/12 patients after 10 weeks of therapy (LCI699C2201, Part 1) and 15/19 patients after 22 weeks of therapy (LCI699C2201, Part II Core). 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. Based on these results osilodrostat is a promising potential new therapy in CS patients.

Study-specific risks

Study-specific risks in study LCI699C1201 include the potential for prolonged periods of uncontrolled hypercortisolism during washout and dose titration with a maximum combined duration of under-treatment of 4 months.

To mitigate the risk of uncontrolled hypercortisolism, specific exclusion criteria and criteria for discontinuation of study treatment with regard to blood pressure and diabetes control are used.

[redacted]

For patients who require washout periods of 4 weeks or longer, treatment with drugs that require a short washout period (e.g., 1 week) is recommended.

Risks of osilodrostat treatment in study population

The risks of treatment with osilodrostat in CS patients include: QT prolongation, 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 men and women. Skin rash has also been observed.

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 Cushing's disease, 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 Cushing's disease trials and has included cases of neutropenia which were associated with mUFC levels that were either below normal or have had a rapid and substantial decline from baseline. In the cases observed, neutropenia has rapidly reversed with discontinuation of osilodrostat, and has also reversed when osilodrostat was continued, typically with decreasing doses.

Mitigation of the risks related to osilodrostat treatment include: frequent study visits with careful monitoring for adverse events and toxicities including those that have been observed in previous studies with osilodrostat; vital signs, blood chemistry including urine, serum, and [redacted], plasma ACTH, electrolytes, renal and liver function, fasting lipid profiles, HbA1c, sex steroid levels (testosterone, estradiol, adrenal androgens), aldosterone and immediate precursor levels, safety ECGs at the time of Cmax and bone metabolism marker.

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. [redacted]

Conclusion

Based on current data, and the planned risk mitigation processes, the overall benefit-risk of trial participation is expected to be positive for all trial subjects

[redacted]

[redacted]

3 Objectives and endpoints

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

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		
To assess the percent change from baseline in the mean Urine Free Cortisol (mUFC) at the individual patient level at Week 12	Percent change from baseline to Week 12 in the mUFC	Refer to Section 10.4.
secondary		
To assess the percent change from baseline in the mUFC at the individual patient level at Week 24 and Week 48	Percent change from baseline to Week 24 and Week 48 in the mUFC	Refer to Section 10.4.4.
To assess the absolute and percent change from baseline in mUFC at Week 12, Week 24 and Week 48	Absolute and percent change from baseline to Week 12, Week 24, and Week 48 in mUFC	Refer to Section 10.4.4.
To assess the complete, partial, and overall response rate at Week 12, Week 24 and Week 48	Complete response rate: proportion of patients with mUFC ≤ ULN at Week 12, Week 24 and Week 48 Partial response rate: proportion of patients with ≥ 50% reduction from baseline in mUFC, but mUFC > ULN at Week 12, Week 24 and Week 48 Overall response rate: proportion of patients with mUFC ≤ ULN or at least 50% reduction from baseline; complete responders or partial responders at Week 12, Week 24 and Week 48	Refer to Section 10.5.2.
To assess the absolute and percent change from baseline in morning serum cortisol at the individual patient level at Week 12, Week 24 and Week 48	Absolute and percent change from baseline to Week 12, Week 24, and Week 48 in morning serum cortisol	Refer to Section 10.5.2.
To assess the absolute and percent change from baseline in morning serum cortisol at Week 12, Week 24 and Week 48	Absolute and percent change from baseline to Week 12, Week 24, and Week 48 in serum cortisol	Refer to Section 10.5.2.
To assess the absolute and percent change from baseline in steroid hormones at the individual patient level at Week 12, Week 24 and Week 48	Absolute and percent change from baseline to Week 12, Week 24, and Week 48 in: serum aldosterone, serum 11-deoxycorticosterone, serum 11-deoxycortisol, serum testosterone, serum estradiol and plasma ACTH	Refer to Section 10.5.2.
To assess the change from baseline in cardiovascular-related metabolic parameters associated with CS at Week 12, Week 24 and Week 48	Absolute and percent change from baseline to Week 12, Week 24, and Week 48 in : fasting glucose, HbA1c, fasting lipid profile, blood pressure, body weight, body mass index (BMI) and waist circumference	Refer to Section 10.5.2.

[redacted]

Objective	Endpoint	Analysis
To assess the general safety of osilodrostat	Adverse events and laboratory abnormalities will be assessed using the Common Terminology Criteria for Adverse Events (CTCAE) grading scale (version 4.03). AEs as reported by the investigator, or by laboratory evaluation, ECG, and Holter recording	Refer to Section 10.5.3.
To assess the change from baseline in Patient-Reported Outcome (Health Related Quality of Life) at individual patient level at Week 12, Week 24 and Week 48	Change in standardized score of CushingQoL and Beck Depression Inventory-II from baseline to Week 12, Week 24 and Week 48	Refer to Section 10.5.7.
To evaluate PK of osilodrostat in patients with CS	Plasma concentrations (at the scheduled time point) of osilodrostat	Refer to Section 10.5.4.
[redacted]		

[redacted]

4 Study design

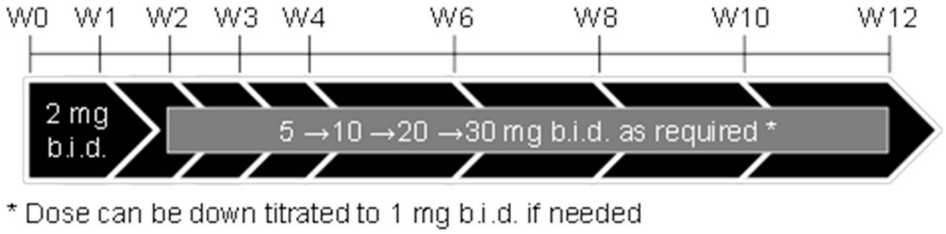
4.1 Description of study design

This is a phase II, single arm, open-label, dose titration, multi-center study consisting of two distinct study periods plus an optional extension period in non-CD patients with CS who have persistent or recurrent hypercortisolism after primary surgery and/or irradiation and/or chemotherapy, and patients *de novo* CS who are not surgical candidates for medical reasons, or refuse to undergo surgery.

Study period I (Week 1 to Week 12):

Study period I is the dose titration period to achieve a stable therapeutic dose and to assess the efficacy and safety of osilodrostat.

Figure 4-1 Study period 1



Dose adjustments are based on the serum cortisol values measured by the local lab at each site. Osilodrostat titration can be done weekly for the initial 4 weeks, up to a maximum dose of 10 mg b.i.d. Two-week interval must be taken to increase from 10 mg b.i.d. to 20 mg b.i.d., even if in initial 4 weeks. After Week 4, the dose can be further increased, if needed, at 2-week intervals (Figure 4-1). The dose is increased if morning serum cortisol is above normal (> ULN of each site). The dose is reduced if serum cortisol is below normal (< LLN of each site), or if the patient is symptomatic and serum cortisol is in the lower part of the normal range. The dose should be maintained if serum cortisol is within the normal range and the patient does not have signs or symptoms of hypocortisolism or adrenal insufficiency.

The mean of three 24-hour UFC (mUFC) values will be measured to evaluate the efficacy in this period.

Study period II (Week 12 to Week 48):

Study period II is the period to assess the sustainability of efficacy and to assess long term safety. For this study period II, only the patients who tolerate and agree to continue osilodrostat treatment will continue study treatment during period II. The patient will be administered with the stable therapeutic dose which will be achieved in the study period I. The dose level could be modified according to the patient condition (refer to Section 6.1 and Section 6.3). The mUFC will also be measured to evaluate the efficacy in this period.

[redacted]

Optional extension period (after Week 48):

Patients who continue to receive clinical benefit, as assessed by the study investigator and who wish to enter the extension period must be re-consented at week 48. Patients who enter the extension period will do so without interruption of study drug or assessments. The extension period will end after all patients have completed Week 72 or discontinued early (prior to Week 72).

Study CLCI699C1201 ends when all ongoing patients have been offered local alternative treatment options; this period will not exceed 9 months after all ongoing patients have completed Week 72.

The patient can either be offered a local alternative treatment option or stay in the study until the study end (i.e. 9 months after the last patient completes Week 72) Patients will complete an EoT visit, and a Follow-up visit (30 days after the last dose administration).

The patient will continue to receive stable therapeutic dose. The dose level could be modified according to the patient condition (refer to Section 6.1 and Section 6.3).

Follow-up

All patients will be contacted for safety evaluation during the 30 days following the last dose of study treatment.

4.2 Timing of interim analyses and design adaptations

The study will have no interim analysis. The data to be reported based on a data cut-off corresponding to the time point where all patients have completed at 12 weeks treatment or discontinued the study for any reason, whichever comes first (including the follow-up period).

4.3 Definition of end of the study

Completion of the study as a whole (last patient last visit) will occur after all patients have completed all assessments as per Table 7-1, Table 7-2 and Table 7-3 or have discontinued early. Study CLCI699C1201 ends when all ongoing patients have been offered local alternative treatment options; this period will not exceed 9 months after all ongoing patients have completed Week 72.

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in Section 7 for a discontinued or withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

[redacted]

5 Population

5.1 Patient population

The study population targets enrollment of 10 adult male or female non-CD patients with CS who have persistent or recurrent hypercortisolism after primary surgery and/or irradiation and/or chemotherapy, and patients with *de novo* CS who are not surgical candidates for medical reasons, or refuse to undergo surgery. This target sample size will be monitored and could be adjusted on the basis of the enrollment status.

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

5.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following general criteria and the criteria applicable for the specific disease causing CS:

Written informed consent must be obtained prior to any screening procedures.

1. Male or female patients aged 18 - 85 years.
2. Patients must have confirmed CS as evidenced by:
    a. For ectopic corticotropin syndrome, patients must have confirmed ectopic corticotropin syndrome by all of the following criteria:
        1. mUFC > 1.3 x ULN [mean of three 24-hour urine samples collected during screening after washout is completed (if patient received medical treatment for hypercortisolism due to CS*) and within a 14-days duration]
        * In case a patient receives steroidogenesis inhibitors and the investigator presumes the patient may meet this mUFC criterion without washout, washout before screening is not mandatory. In case that patient doesn't meet this mUFC criterion without washout, the patient is recommended to be rescreened after washout.
        2. Morning plasma ACTH above lower limit of normal
        3. Low dose (0.5 mg or 1.0 mg p.o. at 23:00) dexamethasone (DEX) suppression test dose not suppress the serum cortisol level at about 8:00 the next morning (i.e. serum cortisol level > 5 μg/dL or > 138 nmol/L for 0.5 mg DEX suppression test, > 3 μg/dL or > 83 nmol/L for 1.0 mg DEX suppression test).
        4. Patients meet any of the following criteria with either i. or ii.:
        i. High dose (8 mg p.o. at 23:00) DEX suppression test dose not suppress the serum cortisol level at about 8:00 the next morning by more than 50%.
        ii. Plasma ACTH does not exceed 1.5 times than pre-dose after corticotropin releasing hormone (CRH) stimulating test.
        5. To exclude pituitary adenoma, patients must meet all of the following criteria:
        - MRI does not confirm pituitary adenoma when MRI data available.
        - Bilateral inferior petrosal sinus sampling (BIPSS) with either CRH or DDVAP stimulation. When the BIPSS data available, the criteria for a non-confirmatory BIPSS test are any of the following:

[redacted]

i. Pre-dose central to peripheral ACTH gradient < 2
ii. Post-dose central to peripheral ACTH gradient < 3

b. For adrenal adenoma, patients must have confirmed adrenal adenoma by all of the following criteria:
   1. mUFC > 1.3 x ULN [mean of three 24-hour urine samples collected during screening, after washout is completed (if patient received medical treatment for hypercortisolism due to CS*), and within a 14-days duration]
      * In case a patient receives steroidogenesis inhibitors and the investigator presumes the patient may meet this mUFC criterion without washout, washout before screening is not mandatory. In case that patient doesn't meet this mUFC criterion without washout, the patient is recommended to be rescreened after washout.
   2. Low plasma ACTH level (< 10 pg/ml or < 2.2 pmol/L)
   3. High dose (8 mg p.o. at 23:00) DEX suppression test dose not suppress the serum cortisol level at about 8:00 the next morning (i.e. serum cortisol level > 5 µg/dL or > 138 nmol/L) when high dose DEX suppression test result available.
   4. Evidence of adrenal tumor by CT and/or MRI
   5. Patients meet any of the following criteria with either i. or ii. :
   i. Patients are not considered for surgery.
   ii. Patients need to control of hypercortisolism before surgery and who can receive 12 weeks treatment.

c. For adrenal carcinoma, patients must have confirmed adrenal carcinoma by all of the following criteria:
   1. mUFC > 1.3 x ULN [mean of three 24-hour urine samples collected during screening, after washout is completed (if patient received medical treatment for hypercortisolism due to CS*), and within a 14-days duration]
      * In case a patient receives steroidogenesis inhibitors and the investigator presumes the patient may meet this mUFC criterion without washout, washout before screening is not mandatory. In case that patient doesn't meet this mUFC criterion without washout, the patient is recommended to be rescreened after washout.
   2. Evidence of adrenal carcinoma by CT and/or MRI and diagnosed as adrenal carcinoma by pathologically and/or clinically
   3. Patients are not considered for surgery.

d. For AIMAH or PPNAD, patients must have confirmed AIMAH or PPNAD by all of the following criteria:
   1. mUFC > 1.3 x ULN [mean of three 24-hour urine samples collected during screening, after washout is completed (if patient received medical treatment for hypercortisolism due to CS*), and within a 14-days duration]
      * In case a patient receives steroidogenesis inhibitors and the investigator presumes the patient may meet this mUFC criterion without washout, washout before screening is not mandatory. In case that patient doesn't meet this mUFC criterion without washout, the patient is recommended to be rescreened after washout.

[redacted]

2. Low plasma ACTH level (< 10 pg/ml or 2.2 pmol/L)
3. High dose (8 mg p.o. at 23:00) DEX suppression test dose not suppress serum cortisol level at about 8:00 the next morning (i.e. serum cortisol level > 5 µg/dL or > 138 nmol/L) when high dose DEX suppression test result available.
4. Evidence of bi-lateral adrenal multiple hyperplasia by CT and/or MRI (large nodules for AIMAH and small nodules for PPNAD).
5. Patients are not considered for surgery.

3. Patients are expected to remain in stable condition for at least 5 months. [e.g. controlled condition for the primary disease (i.e. tumor of the patients.)]
4. For patients on medical treatment for hypercortisolism due to CS the following washout periods must be completed prior to baseline efficacy assessments:
   a. Steroidogenesis inhibitors (metyrapone, trilostane, ketoconazole): 1 week
   b. Mitotane: 6 months
   c. Mifepristone: 4 weeks
   d. Other experimental therapy: at least 5 half-lives or 30 days, whichever is longer

5.3 Exclusion criteria

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

1. Patients with Cushing's disease
2. History of hypersensitivity to osilodrostat or to drugs of similar chemical classes
3. Patients who have a known inherited syndrome as the cause for hormone over secretion [i.e. Carney Complex, McCune-Albright syndrome, multiple endocrine neoplasia I (MEN-1), aryl hydrocarbon receptor interacting protein (AIP)]. **This exclusion criterion is retired as of Amendment #2.**
4. History of malignancy of any organ system [with the exception of: a) malignancy causing ectopic corticotripin syndrome, or b) localized basal cell carcinoma of the skin], treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases
5. Patients receiving treatment for malignancy (e.g., cytotoxic chemotherapy, molecular targeting drugs, somatostatin analogue) within 4 weeks or ≤ 5 x half-life of the agent (whichever is longer) before first dose of osilodrostat
6. Patients with risk factors for QTc prolongation or Torsades de Pointes, including:
   - Patients with a baseline QTcF > 450 ms for males and QTcF > 460 ms for females, personal or family history of long QT syndrome, or concomitant medications known to prolong the QT interval
   - Hypokalemia, hypocalcaemia, or hypomagnesaemia, if NOT corrected before pre-dose Day 1
7. Diabetic patients with poorly controlled diabetes as evidenced by HbA1c > 9%
8. Patients who have a history of: congestive heart failure (NYHA Class III or IV), unstable angina, sustained ventricular tachycardia, clinically significant bradycardia, advanced heart block, acute myocardial infarction less than one year prior to study entry, or clinically significant impairment in cardiovascular function

[redacted]

9. Patients with moderate to severe renal impairment [estimated glomerular filtration rate (GFR) < 60 mL/min by the MDRD formula, or serum creatinine > 2.0 x ULN]
10. Patients with liver disease such as cirrhosis, chronic active hepatitis, or chronic persistent hepatitis, or patients with any of the following laboratory abnormalities;
    - Total bilirubin > 1.5 x ULN
    - Aspartate transaminase (AST) > 3.0 x ULN
    - Alanine transaminase (ALT) > 3.0 x ULN
11. Patients who are not euthyroid judged by the investigator
12. Patients who have undergone major surgery within 1 month prior to screening
13. Pregnant or nursing (lactating) women
14. 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 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 bilateral oophorectomy, documentation is required (e.g. operative report, pelvic ultrasound or other reliable imaging method).
    - Male sterilization (at least 6 months prior to screening). For female subjects on the study the vasectomized male partner should be the sole partner for that subject.
    - Combination of any two of the following (a+b or a+c, or b+c):
        a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception
        b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
        c. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

      In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

      Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks ago. In the case of bilateral oophorectomy, documentation is required (e.g. operative report, pelvic ultrasound or other reliable imaging method).
15. Patients who have any current or prior medical condition that can interfere with the conduct of the study or the evaluation of its results in the opinion of the investigator or the sponsor's medical monitor
16. Patients who have a history of alcohol or drug abuse in the 6 months period prior to study treatment

[redacted]

17. Patients with a history of non-compliance to medical regimens or who are considered potentially unreliable or will be unable to complete the entire study

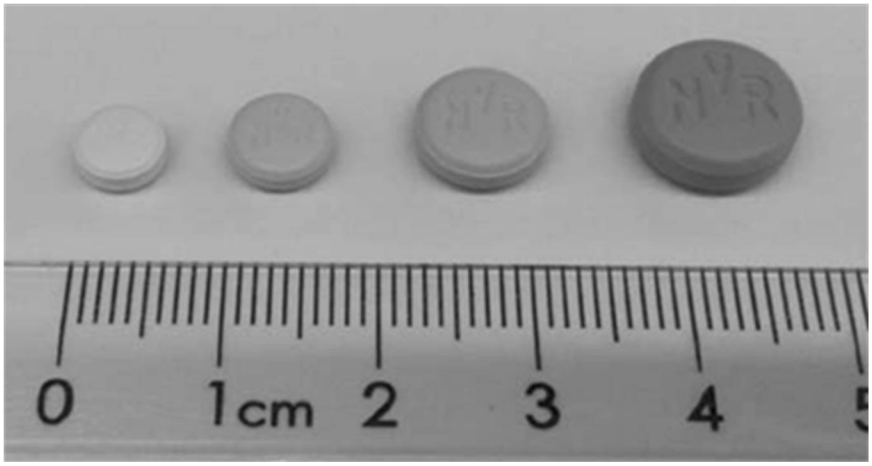
6 Treatment

6.1 Study treatment

Study treatment: osilodrostat 1 mg, 5 mg, 10 mg, 20 mg in the form of film-coated tablets for oral administration: On 22-Aug-2016 (before Amendment #2), the 20 mg tablet strength was discontinued for use in the trial, in order to reduce the risk of dosing error in which the patient took more than the prescribed dose. Remaining supplies of the 20 mg tablets were to be collected from the sites.

Each strength has a unique size and color (Figure 6-1). The osilodrostat 1 mg, 5 mg, 10 mg and 20 mg film coated tablets are approximately 6 mm, 7 mm, 9 mm, and 11 mm respectively in diameter and pale yellow, yellow, pale orange brown and light brown respectively in color.

Figure 6-1 Appearance of osilodrostat tablets by strength



Legend: Each strength of osilodrostat has a unique size and color to aid in recognition. The appearance of the actual tablets may vary slightly from the picture.

6.1.1 Dosing regimen

The dosing regimen of osilodrostat in the planned study will be titrated according to the following escalation sequence: osilodrostat 2 mg b.i.d., 5 mg b.i.d., 10 mg b.i.d., 20 mg b.i.d., and 30 mg b.i.d.. If hypocortisolism occurs at 2 mg b.i.d., the dose can be lowered to 1 mg b.i.d.. The maximum dose of osilodrostat in this study is 30 mg b.i.d..

Dose adjustments are based on the serum cortisol values as measured by the local lab at each site. The osilodrostat dose is increased if the morning serum cortisol is above normal (> ULN of each site). The dose titration based on the mUFC value from central analysis could be considered with the same scheme (> ULN). Osilodrostat titration can be done weekly for the initial 4 weeks, up to a maximum dose of 10 mg b.i.d.. Two-week interval must be taken to increase from 10 mg b.i.d. to 20 mg b.i.d., even if in initial 4 weeks. After Week 4, the dose can be further increased, if needed, at 2-week intervals. The osilodrostat dose will be reduced if the

serum cortisol value is < LLN of each site or the patient has signs and symptoms of hypocortisolism or adrenal insufficiency and the serum cortisol value is in the lower part of the normal range. The osilodrostat dose will be maintained if the serum cortisol value is in the normal range and the patient does not have signs or symptoms of hypocortisolism or adrenal insufficiency.

If hypocortisolism occurs at 2 mg b.i.d., the dose can be decreased to 1 mg b.i.d. or lower, e.g., 1 mg q.d. (once a day) or 1 mg q.o.d. (every other day), if needed. Any lower dose other than 1 mg bid is not a standard dose and as mentioned below must be discussed with the sponsor on a case-by-case basis before implementation.

Once the patient is controlled following the dose titration period, if intermediate doses (doses that are not specified in the titration sequence) are deemed necessary, the same dose should be used in the a.m. and the p.m., as a b.i.d. regimen, if possible, to ensure consistent drug exposure.

Permitted intermediate dose levels are: 3, 7 and 15 mg b.i.d.

Outside of the planned doses for the escalation sequence and permitted intermediate doses, any dosing regimen not following the above must be discussed with the sponsor on a case-by-case basis.

Osilodrostat should be administered at approximately the same time each day, about 12-hours apart for the twice-daily regimen. Osilodrostat can be administered regardless of food or fast condition.

On study visit days, patients should be reminded not to take the study treatment prior to the site visit in order to ensure compliance with the pre-dose PK sampling procedure. The morning dose on the visit days should be taken at the site after the pre-dose PK sampling.

Dose reductions and temporary dose interruptions for safety reasons are permitted at any time during the study.

6.1.2 Ancillary treatments

Not applicable

6.1.3 Rescue medication

Not applicable

6.1.4 Guidelines for continuation of treatment

Osilodrostat therapy is continued unless it must be interrupted, discontinued for safety or other reason, or completion of study treatment. See Section 6.1.5 “Treatment duration” and Section 6.3 “Dose modifications” for details.

6.1.5 Treatment duration

The primary endpoint is assessed at Week 12 but treatment duration is 48 weeks in patients who agree to continue after Week 12. In addition, patients will have the option to continue in the extension phase; patients who wish to enter the extension period must be re-consented at week 48. The optional extension period will end when all patients have completed Week 72 or discontinued early (prior to Week 72).

Study CLCI699C1201 ends when all ongoing patients have been offered local alternative treatment options; this period will not exceed 9 months after all ongoing patients have completed Week 72.

The patient can either be offered a local alternative treatment option or stay in the study until the study end (i.e. 9 months after the last ongoing patient completes Week 72). Patients will complete an EOT visit and a Follow-up visit (30 days after the last dose administration).

In the absence of premature discontinuation, patients will receive osilodrostat for a minimum of 12 weeks.

6.2 Dose escalation guidelines

Not applicable. This is not a dose escalation study. Please refer to Section 6.1.1 for dose titration procedure.

6.3 Dose modifications

6.3.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions are either recommended or mandated in order to allow patients to continue the study treatment.

These dose modifications are summarized in Table 6-1 and Table 6-2. Deviations to mandatory dose modifications are not allowed. Permanent treatment discontinuation is mandatory for specific events indicated as such in Table 6-2 or listed in Section 7.1.4.

During treatment with osilodrostat in patients with Cushing's syndrome and regardless of suspected drug causality, an AE may require not only interruption of study drug, but also replacement or stress doses of glucocorticoids until the AE has resolved.

Please refer to Section 4.1 "Description of study design" and Section 6.1.1 "Dosing regimen" for further information about dose and dosing regimen during various periods during the trial.

Symptomatic hypocortisolism or adrenal insufficiency is suspected on the basis of clinical signs/symptoms, which may include gastrointestinal symptoms (nausea, vomiting), fatigue, weakness, failure to thrive, morning headache, symptoms consistent with hypoglycemia, dizziness. When symptomatic hypocortisolism is suspected, the investigator may order urgent local laboratory testing, including serum cortisol to help differentiate glucocorticoid withdrawal symptoms from adrenal insufficiency.

For patients whose dose needs to be fine-tuned to provide the requested efficacy or are unable to tolerate the protocol-specified dosing schedule, dose adjustments to other than standard dose levels (2, 5, 10, 20 and 30 mg respectively b.i.d) are permitted in order to keep the patient on study drug. The following guidelines (Table 6-1 and Table 6-2) need to be applied. These changes must be recorded on the Dosage Administration Record CRF.

Table 6-1 Dose Modification Guidelines for osilodrostat-suspected toxicities

Toxicity	Actions
Symptomatic hypocortisolism or adrenal insufficiency	Recommendation: If the investigator at any time suspects symptomatic 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 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 serum cortisol or mUFC is 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 serum cortisol or mUFC is normal or > ULN.
Persistent asymptomatic hypocortisolism (serum cortisol or mUFC < LLN) at the lowest dose of osilodrostat (1 mg every other day)	Recommendation: The investigator can interrupt study drug and restart at the same dose as clinically indicated.
Glucocorticoid withdrawal syndrome	Recommendation: The investigator can reduce or interrupt dose until improved
Hypotension (mild, reversible)	Recommendation: The investigator can reduce or interrupt dose until improved.
Hypertension	Recommendation: The investigator can reduce or interrupt dose until improved; consider ACE inhibitors for treatment of hypertension, or spironolactone as second line treatment, particularly if hypokalemia is present. **ACE inhibitors and spironolactone should not be used in combination.**
Weight gain, edema	Recommendation: The investigator can reduce or interrupt dose until improved; consider spironolactone for treatment of edema.
Hypokalemia	Recommendation: The investigator can reduce or interrupt dose until improved; replace potassium; consider spironolactone or eplerenone for prevention and treatment of hypokalemia
Hyperkalemia	Recommendation: The investigator can reduce or interrupt dose until improved; if on spironolactone or eplerenone, reduce or interrupt; treat with kayexalate and other therapies as needed.
Hirsutism (women only)	Recommendation: The investigator can reduce or interrupt dose until improved; review testosterone level; consider spironolactone, cyproterone acetate or finasteride per local guideline.
Acne (women or men)	Recommendation: The investigator can reduce or interrupt dose until improved; review testosterone level; consider spironolactone, cyproterone acetate or finasteride per local guideline.
Abbreviations: UFC, 24-hour urine free cortisol; ULN, upper limit of the normal reference range; LLN, lower limit of the normal reference range.	

Instructions for monitoring liver function, and the criteria for interrupting, re-initiating, reducing dose or discontinuation of study medication are provided in Table 6-2 below.

[redacted]

Table 6-2 Criteria for interruption and re-initiation of osilodrostat for abnormal liver function

Isolated total Bilirubin elevation	
> ULN – 1.5 x ULN	Recommendation: Maintain dose level
> 1.5 - 3.0 x ULN	Recommendation: Interrupt study drug dose. Monitor liver function tests (LFTs)a weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN: If resolved in ≤ 14 days, restart study drug and maintain dose level If resolved in > 14 days, restart study drug and decrease by one dose level
> 3.0 - 10.0 x ULN*	Recommendation: Interrupt study drug. Monitor LFTs[a] weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN: If resolved in ≤ 14 days, restart study drug and decrease by one dose level Mandatory: 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*	Mandatory: 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	Recommendation: Maintain dose level
> 3.0 - 5.0 x ULN	Recommendation: 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	Recommendation: Interrupt 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 Mandatory: If not resolved after 4 weeks, discontinue patient from study drug
> 10.0 x ULN	Mandatory: 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.

[redacted]

<table>
<tr><td colspan="2">Isolated total Bilirubin elevation</td></tr>
<tr><td colspan="2">Combined [b,c] elevations of AST or ALT and total bilirubin</td></tr>
<tr><td>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 > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [total bilirubin > 2 x baseline AND > 2.0 x ULN]</td><td>Mandatory: 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 6.3.2.1 for additional follow-up evaluations as applicable.</td></tr>
<tr><td colspan="2">All dose modifications should be based on the worst preceding toxicity.
a. Core LFTs consist of ALT, AST, GGT, total bilirubin (fractionated [direct and indirect], if total bilirubin > 2.0 x ULN), and alkaline phosphatase (ALP) (fractionated [quantification of isoforms], if alkaline phosphatase > 2.0 x ULN.)
b. “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 study drug at the situation when interrupt study drug is needed for one parameter and discontinue study drug 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
c. “Cholestasis” defined as: ALP elevation (> 2 x ULN and R value (ALT/ALP in x ULN) < 2) in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis.
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.</td></tr>
</table>

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 patient should be observed. If mUFC rises to above the ULN, and has been off glucocorticoid therapy for at least one week, osilodrostat may be re-started.

If the patient has interruption of osilodrostat for more than 4 weeks, the investigator should consider early discontinuation from the study. Patients that had interruption of osilodrostat and mUFC remains ≤ ULN off osilodrostat should remain on study for observation.

These changes must be recorded on the Dosage Administration Record CRF.

[redacted]

6.3.2 Follow-up for toxicities

Please refer to Section 6.3.1 and Section 8.1.3.

6.3.2.1 Follow-up on potential drug-induced liver injury (DILI) cases

Transaminase increase combined with total bilirubin (TBIL) increase may be indicative of potential DILI, and should be considered as clinically important event.

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.

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 ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury.

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 tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

- Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/ international normalized ratio (INR) and alkaline phosphatase.
- 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.
- Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.
- Obtain PK sample, as close as possible to last dose of study drug.
- 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 8.2.1) and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

6.3.3 Anticipated risks and safety concerns of the study drug

Anticipated drug-related risks are summarized in Section 2.6. Recommended guidelines for supportive treatment for expected toxicities, including management of study-drug induced adverse events, are provided in Section 6.3.1.

Additional anticipated risks are summarized in Section 8.1.3 "Adverse events of special interest." Two of these AEs are described in greater detail: the potential for QT prolongation (Section 8.1.3.1), and hypocortisolism (glucocorticoid withdrawal/adrenal insufficiency) (Section 8.1.3.2). Recommendations for QT prolongation monitoring and management are provided in Section 7.2.2.7. Other AEs of special interest for osilodrostat (either reported or anticipated based on the mechanism of action of the drug) include cardiac arrhythmia. These particular AEs may require premature discontinuation from the study (see Section 7.1.4).

Refer to preclinical toxicity and or clinical data found in the [Investigator's Brochure].

6.4 Concomitant medications

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 patient 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 patient signs the informed consent through 30 days after the last dose of osilodrostat must be listed on the CRF. If the patient receives the new treatment for Cushing's syndrome within 30 days from the study treatment discontinuation, from that point, only the concomitant medication and significant non-drug therapies which are used for adverse events should be recorded.

All prescription medications and over-the-counter drugs taken within the timeframe defined in the entry criteria prior to the start of the study, must be recorded on the prior medication page of the CRF. Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation dates and the reason for therapy.

All concomitant medications received during the study should be reported on the CRF, and include the drug name (specific trade name), start and discontinuation dates and the reason for therapy. Medications used for the treatment of hypertension, diabetes or impaired glucose tolerance, and hyperlipidemia, in particular, require this detailed information as part of the efficacy assessment.

6.4.1 Permitted concomitant therapy

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug including herbal/natural medications) and significant non-drug therapies (including physical therapy and blood transfusions) administered during the study must be listed on the concomitant medications or the surgical and medical procedures CRF.

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

[redacted]

monitoring for the risk of severe hyperkalemia, which is further increased if renal insufficiency is present.

Medications that are metabolized by CYP450 enzymes

In vitro drug metabolism studies show that osilodrostat 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 drug-drug interaction (DDI) study, osilodrostat 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 2) should be used with caution.

The patient 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 osilodrostat should be discontinued according to investigators' judgement.

6.4.2 Prohibited concomitant therapy

Use of the following concomitant medications are prohibited during the study:

- Other drug treatments for Cushing's syndrome
- 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 (e.g., prednisone, prednisolone, and dexamethasone) may be used as required for the short-term treatment of symptomatic 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 osilodrostat, weaning and discontinuation of glucocorticoid therapy, or early discontinuation from the study.

Topical and ophthalmic administrations are acceptable to use during the study.

6.4.2.1 Concomitant medications with a "Known risk to cause TdP" and drugs with a "Possible risk to cause TdP"

Preclinical and clinical data indicate that there is a risk of QTc prolongation in humans (see Section 8.1.3.1). Therefore, the use of medications with a "known risk to cause TdP" and with a "possible risk to cause TdP" concomitantly with osilodrostat is prohibited.

If a patient requires a long-term medication from the two categories mentioned above, and there is no appropriate alternative medication available, then they should be discontinued from the study.

[redacted]

However, if a patient requires such a drug for short-term therapy, e.g., antibiotics for active infection, then the osilodrostat may be interrupted temporarily while this drug is administered after a thorough risk-benefit assessment. This does not require the patient to discontinue from the study prematurely. Washout periods for osilodrostat 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 osilodrostat therapy in the investigator's judgment. In such cases, a discussion with the Novartis medical monitor is recommended.

Please refer to Appendix 3 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 Novartis Medical Monitor when considering the use of medications with a "known risk to cause TdP" and with a "possible risk to cause TdP".

6.5 Patient numbering

Each patient 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 patient throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each 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 to the investigator through the Oracle Clinical RDC interface.

6.6 Study drug preparation and dispensation

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

Study drug use in this study includes 1 mg, 5 mg, 10 mg and 20 mg tablets: On 22 Aug 2016 (before Amendment #2), the 20 mg tablet strength was discontinued for use in the trial, in order to reduce the risk of dosing error in which the patient took more than the prescribed dose. Remaining supplies of the 20 mg tablets were to be collected from the sites. There is a unique size and color for each dose strength (see Figure 6-1). Study drug is dispensed in a set of kits (bottles) for each patient at each visit. Osilodrostat is dispensed in separate bottles for each dose strength. The label on each bottle indicates the dose strength.

Patients may be dispensed bottles of more than one tablet strength at the same visit. For example, if a patient is on the preferred intermediate dose of 7 mg b.i.d., the patient would be provided with both 1 mg and 5 mg tablet strengths and instructed to take 2 x 1 mg tablets and a 1 x 5 mg tablet, twice a day. Consequently, to ensure patient safety, it is **very important** that site staff educate the patient on how to recognize the tablet strength dispensed at each visit, both on the bottle labels, and by the appearance of tablets by dose strength. Patients are given a dosing card that includes general instructions and an image displaying the color and size of each tablet strength. Clear, simple, written instructions must be provided to the patient at the visit; these instructions must include the dose and the number of tablets of each strength to be taken in the morning and in the evening. The site ensures that enough study drug is dispensed to treat

[redacted]

the patient until the next scheduled visit by specifying the set of kits (bottles) for each patient at each visit. A minimal number of strengths will be dispensed at any one visit, as feasible.

Patients requiring a different tablet strength to implement a dose change between scheduled study visits, will need to return to the site (unscheduled visit) to collect the new study drug supplies. The site will dispense the corresponding kit(s) to the patient, to provide drug supply until the next study visit.

Table 6-3 Preparation and dispensing

Study treatments	Dispensing	Preparation
Osilodrostat (1 mg, 5 mg, 10 mg and 20 mg)	Tablets including instructions for administration are dispensed by study personnel on an outpatient basis. Patients will be provided with adequate supply of study drug for self-administration at home until at least their next scheduled study visit (including any dose change required in between visits). **More than one tablet strength may be dispensed to patients at the same visit.**	Not applicable

6.6.1 Study drug packaging and labeling

Osilodrostat will be supplied as 1 mg, 5 mg, and 10 mg film coated tablets (the 20 mg tablet strength was discontinued for use), and will be given orally twice a day.

Each study site will be supplied by Novartis with study drug. Medication labels will be in the local language and comply with the legal requirements of Japan. They will include storage conditions for the drug (for details, see study drug handling procedure which is provided by Novartis).

6.6.2 Drug supply and storage

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

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

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

6.6.3.2 Study drug accountability

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

[redacted]

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

6.6.3.3 Handling of other study treatment

Not applicable

6.6.4 Disposal and destruction

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

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1, Table 7-2 and Table 7-3 list all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation.

No CRF will be used as a source document.

The table indicates which assessments produce data to be entered into the clinical database (D) or remain in source documents only (S) ("Category" column). Patients who discontinue study treatment except for planned discontinuation of study treatment at Week 12 or Week 48, should be scheduled for a visit as soon as possible. Whenever patients discontinue study treatment (before or at Week 12 [during study period I], before or at Week 24 [during study period II] or during optional extension period), all of the assessments listed for the EoT visit will be performed.

Table 7-1 Visit evaluation schedule – Study period I (dose titration period) and Study period II

			Screening Phase		Treatment phase																		
	Category	Protocol Section	Screening	Baseline	Study period I (dose titration period)									Study period II									
Day			**-35 ~ -8**	**-7 ~ -1**	**1**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	**113**	**141**	**169**	**183**	**211**	**239**	**253**	**281**	**309**	**337**
Week			**-5 ~- 2**	**-1**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**26**	**30**	**34**	**36**	**40**	**44**	**48**
Obtain informed consent	D	7.1.1	X										X										X
Patient history																							
Demography	D	7.1.1.3	X																				
Inclusion/exclusion criteria	D	5.2, 5.3	X	X																			
Medical History	D	7.1.1.3	X																				
CS History	D	7.1.1.3	X																				
Prior treatments for CS	D	7.1.1.3	X																				
Concomitant medications	D	7.1.1.3	As required																				
Physical examination	S	7.2.2.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body height	D	7.2.2.3	X																				
Body weight	D	7.2.2.3	X	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Waist circumference	D	7.2.2.3	X	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs																							
Body temperature	D	7.2.2.2	X	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood pressure/Pulse rate	D	7.2.2.2	X	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory assessments																							
Hematology	D	7.2.2.4.1	X	X					X		X		X	X	X	X	X	X	X	X	X	X	X
Chemistry	D	7.2.2.4.2	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[redacted]

			Screening Phase		Treatment phase																	
	Category	Protocol Section	Screening	Baseline	Study period I (dose titration period)									Study period II								
Day			**-35 ~ -8**	**-7 ~ -1**	**1**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	**113**	**141**	**169**	**183**	**211**	**239**	**253**	**281**	**309**	**337**
Week			**-5 ~- 2**	**-1**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**26**	**30**	**34**	**36**	**40**	**44**	**48**
Thyroid Panel	D	7.2.2.4.5		X									X			X			X				X
Luteinizing Hormone (LH) and Follicle stimulating hormone (FSH)	D	7.2.2.4.6		X									X			X			X				X
Coagulation	D	7.2.2.4.4		X									X										X
Bone metabolism marker	D	7.2.2.4.7		X						X			X			X							X
Urinalysis	D	7.2.2.4.3	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (serum)	D	7.2.2.4.8	X	X																			
Pregnancy test (urine)	D	7.2.2.4.8				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy assessments																							
24-hour urinary free cortisol and creatinine	D	7.2.1	X	X					X		X		X			X							X
Serum testosterone and estradiol	D	7.2.2.4.6		X									X			X			X				X
Serum cortisol (central and local)	D	7.2.2.4.6		X		X	X	X	X	X	X	X	X	X	X	X			X				X
Plasma ACTH	D	7.2.2.4.6		X			X		X	X	X	X	X	X	X	X			X				X
Serum 11-deoxycortisol	D	7.2.2.4.6		X			X						X			X			X				X
Serum aldosterone	D	7.2.2.4.6		X			X			X		X	X			X			X				X
[redacted]																							
Serum 11-Deoxycorticosterone	D	7.2.2.4.6		X			X						X			X			X				X

[redacted]

			Screening Phase		Treatment phase																	
	Category	Protocol Section	Screening	Baseline	Study period I (dose titration period)									Study period II								
Day			**-35 ~ -8**	**-7 ~ -1**	**1**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	**113**	**141**	**169**	**183**	**211**	**239**	**253**	**281**	**309**	**337**
Week			**-5 ~- 2**	**-1**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**26**	**30**	**34**	**36**	**40**	**44**	**48**
Fasting serum insulin	D	7.2.2.4.7		X									X			X			X				X
HbA1C	D	7.2.2.4.7	X	X									X			X			X				X
Safety																							
Adverse events	D	8.1	As required																				
12-lead safety ECG assessment	D	7.2.2.6	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead 24-hour Holter ECG recording	D	7.2.2.6		X			X						X			X							X
CT/MRI for ectopic corticotropin syndrome	D	7.2.2.5	X										X										X
Questionnaires of health related quality of life	D	7.2.6		X					X		X		X			X							X
[redacted]																							
Study drug administration	D	6.1.1			Continuous b.i.d. dosing																		
PK sampling	D	7.2.3			X	X	X	X	X	X	X	X	X	X	X	X							X

[redacted]

Table 7-2 Visit evaluation schedule – Study extension period (Year 1)

			Treatment phase							
	Category	Protocol Section	Optional extension period							
Day			**365**	**393**	**421**	**449**	**477**	**505**	**589**	**673**
Week			**52**	**56**	**60**	**64**	**68**	**72**	**84**	**96**
Obtain informed consent	D	7.1.1								
Patient history										
Concomitant medications	D	7.1.1.3	As required							
Physical examination	S	7.2.2.1	X	X	X	X	X	X	X	X
Body weight	D	7.2.2.3	X	X	X	X	X	X	X	X
Waist circumference	D	7.2.2.3	X	X	X	X	X	X	X	X
Vital signs										
Body temperature	D	7.2.2.2	X	X	X	X	X	X	X	X
Blood pressure/Pulse rate	D	7.2.2.2	X	X	X	X	X	X	X	X
Laboratory assessments										
Hematology	D	7.2.2.4.1	X	X	X	X	X	X	X	X
Chemistry	D	7.2.2.4.2	X	X	X	X	X	X	X	X
Thyroid Panel	D	7.2.2.4.5			X			X	X	X
Luteinizing Hormone (LH) and Follicle stimulating hormone (FSH)	D	7.2.2.4.6			X			X	X	X
Coagulation	D	7.2.2.4.4			X			X	X	X
Bone metabolism marker	D	7.2.2.4.7								
Urinalysis	D	7.2.2.4.3			X			X	X	X
Pregnancy test (urine)	D	7.2.2.4.8			X			X	X	X
Efficacy assessments										
24-hour urinary free cortisol and creatinine	D	7.2.1								
Serum testosterone and estradiol	D	7.2.2.4.6			X			X	X	X

[redacted]

			Treatment phase							
	Category	Protocol Section	Optional extension period							
Day			**365**	**393**	**421**	**449**	**477**	**505**	**589**	**673**
Week			**52**	**56**	**60**	**64**	**68**	**72**	**84**	**96**
Serum cortisol (central and local)	D	7.2.2.4.6			X			X	X	X
Plasma ACTH	D	7.2.2.4.6			X			X	X	X
Serum 11-deoxycortisol	D	7.2.2.4.6			X			X	X	X
Serum aldosterone	D	7.2.2.4.6			X			X	X	X
[redacted]										
Serum 11-Deoxycorticosterone	D	7.2.2.4.6			X			X	X	X
Fasting serum insulin and HbA1C	D	7.2.2.4.7			X			X	X	X
Safety										
Adverse events	D	8.1	As required							
12-lead safety ECG assessment	D	7.2.2.6			X			X	X	X
12lead 24-hour Holter ECG recording	D	7.2.2.6						X		
CT/MRI for ectopic corticotropin syndrome	D	7.2.2.5								X
Questionnaires of health related quality of life	D	7.2.6						X		X
[redacted]										
Study drug administration	D	6.1.1	Continuous b.i.d dosing							
PK sampling	D	7.2.3								

[redacted]

Table 7-3 Visit evaluation schedule – Study extension period (After Year 1)

			Treatment phase						
	Category	Protocol Section	Optional extension period					EoT	Follow-up
Day			**757**	**841**	**925**	**1009**	**1093, 1177, 1261, ...**	**85/337/NA**	
Week			**108**	**120**	**132**	**144**	**156, 168, 180, ...(every 12 weeks)**	**12/48/premature withdrawal**	**30 days from last dose**
Obtain informed consent	D	7.1.1							
Patient history									
Concomitant medications	D	7.1.1.3	As required						
Physical examination	S	7.2.2.1	X	X	X	X	X	X	X
Body weight	D	7.2.2.3	X	X	X	X		X	X
Waist circumference	D	7.2.2.3	X	X	X	X		X	X
Vital signs									
Body temperature	D	7.2.2.2	X	X	X	X	X	X	X
Blood pressure/Pulse rate	D	7.2.2.2	X	X	X	X		X	X
Laboratory assessments									
Hematology	D	7.2.2.4.1	X	X	X	X	Same Extension assessments will be performed with same frequency.	X	X
Chemistry	D	7.2.2.4.2	X	X	X	X		X	X
Thyroid Panel	D	7.2.2.4.5		X		X		X Only up to Week 48	X
Luteinizing Hormone (LH) and Follicle stimulating hormone (FSH)	D	7.2.2.4.6		X		X		X Only up to Week 48	X
Coagulation	D	7.2.2.4.4	X	X	X	X		X	X
Bone metabolism marker	D	7.2.2.4.7						X Only at Week 6, 12, 24 or 48	
Urinalysis	D	7.2.2.4.3	X	X	X	X		X	X

[redacted]

	Category	Protocol Section	Treatment phase						
			Optional extension period					EoT	Follow-up
Day			**757**	**841**	**925**	**1009**	**1093, 1177, 1261, ...**	**85/337/NA**	
Week			**108**	**120**	**132**	**144**	**156, 168, 180, ...(every 12 weeks)**	**12/48/premature withdrawal**	**30 days from last dose**
Pregnancy test (urine)	D	7.2.2.4.8	X	X	X	X	Same Extension assessments will be performed with same frequency.	X	X
Efficacy assessments									
24-hour urinary free cortisol and creatinine	D	7.2.1					Same Extension assessments will be performed with same frequency.	X Only up to Week 48	
Serum testosterone and estradiol	D	7.2.2.4.6		X		X		X	X
Serum cortisol (central and local)	D	7.2.2.4.6	X	X	X	X		X	X
Plasma ACTH	D	7.2.2.4.6	X	X	X	X		X	X
Serum 11-deoxycortisol	D	7.2.2.4.6		X		X		X Only up to Week 48	X
Serum aldosterone	D	7.2.2.4.6		X		X		X Only up to Week 48	X
[redacted]									
Serum 11-Deoxycorticosterone	D	7.2.2.4.6	X	X	X	X		X Only up to Week 48	X
Fasting serum insulin and HbA1C	D	7.2.2.4.7		X		X		X Only up to Week 48	X
Safety									

[redacted]

	Category	Protocol Section	Treatment phase						
			Optional extension period					EoT	Follow-up
Day			**757**	**841**	**925**	**1009**	**1093, 1177, 1261, ...**	**85/337/NA**	
Week			**108**	**120**	**132**	**144**	**156, 168, 180, ...(every 12 weeks)**	**12/48/premature withdrawal**	**30 days from last dose**
Adverse events	D	8.1	As required						
12-lead safety ECG assessment	D	7.2.2.6	X	X	X	X	Same Extension assessments will be performed with same frequency.	X	X
12lead 24-hour Holter ECG recording	D	7.2.2.6		X				X	
CT/MRI for ectopic corticotropin syndrome	D	7.2.2.5				X	Same Extension assessments will be performed with same frequency.	X	
Questionnaires of health related quality of life	D	7.2.6						X	
[redacted]									
Study drug administration	D	6.1.1	Continuous b.i.d dosing						
PK sampling	D	7.2.3						X Only up to Week 48	

[redacted]

7.1.1 Screening

Written main informed consent must be obtained before any study specific assessments are performed.

The screening assessments must be performed within 35 days before planned patient's eligibility confirmation and before the start of the first study drug dose of osilodrostat at Day 1.

Based on the central laboratory turnaround time, it is highly recommended to send the three 24-hour urinary free cortisol samples to the central Laboratory at least 14 days prior to Day 1 in order to ensure that sufficient time is allowed for central laboratory results to become available.

Eligibility is assessed based on the screening results collected at the screening visit.

For laboratory evaluations used to determine eligibility, a repeated evaluation within the screening window is permitted for screening results out of the defined range. If the repeated laboratory result meets the criteria, that result may be used to determine eligibility. If the repeated laboratory result does not meet the criteria, the patient will be considered a screening failure. In this case, the subject will not be required to sign another ICF.

A new ICF will need to be signed if the investigator chooses to re-screen the patient after a patient has screen failed. The rescreening should be documented in the source files and using the same Patient Number.

An individual patient may only be rescreened once for the study. Once the number of patients screened and enrolled is likely to ensure target enrollment, the Sponsor may close the study to further screening. In this case the patients who screen failed will not be permitted to re-screen. For details of assessments, refer to Table 7-1.

[redacted]

7.1.1.1 Eligibility screening

Patient eligibility will be checked by the sponsor once all screening procedures are completed. The eligibility check form will be sent from the site to the sponsor for evaluation. Upon confirmation of eligibility, the Sponsor will return the signed eligibility check form to the site. The investigator site will then be allowed to assign treatment to the patient.

7.1.1.2 Information to be collected on screening failures

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the screening phase disposition page. The demographic information, informed consent, and inclusion/exclusion pages must also be completed for screen failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a serious adverse event during the screening phase.

[redacted]

7.1.1.3 Patient demographics and other baseline characteristics

Standard demographic information and medical history will be collected. Baseline assessments will be collected as per Table 7-1. For the CS history, the listed items in the inclusion criteria will be collected.

7.1.2 Run-in period

Although there is no run-in period, washout requirements as described in inclusion criteria (Section 5.2) must be followed.

7.1.3 Treatment period

Treatment period is divided into 3 study periods (Study period 1, Study period 2 and Extension period). For details of assessments, refer to Table 7-1, Table 7-2 and Table 7-3.

Patients should be seen for all visits on the designated day with a visit window of ± 3 days and in a fasting state except for Day 1.

During Study period 1, patient will come to site every week for initial 4 weeks and every 2 weeks thereafter. During Study period 2 and Extension period, patient will come to site according to the schedule indicated in Table 7-1, Table 7-2 and Table 7-3.

7.1.4 Discontinuation of study treatment

Patients may voluntarily discontinue from the study treatment for any reason at any time. If a patient decides to discontinue from the study treatment, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information in the patient's chart and on the appropriate CRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reasons.

The investigator may discontinue study treatment for a given patient if, he/she believes that continuation would be detrimental to the patient's well-being.

Study treatment must be discontinued under the following circumstances (Refer to Table 6-1 and Table 6-2):

- 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 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 sodium < 130 mmol/L)

[redacted]

  - Isolated total Bilirubin elevation > 10.0 x ULN, or > 3.0 - 10.0 x ULN not resolved after 14 days
  - Isolated AST or ALT elevation > 10.0 x ULN, or > 5.0 - 10.0 x ULN not resolved after 4 weeks
  - 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
  - For patients with elevated baseline AST or ALT or total bilirubin value: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [total bilirubin > 2 x baseline AND > 2.0 x ULN]
- QTcF > 500 msec, if confirmed by cardiologist review (see Section 7.2.2.7)
- QTcF > 480 msec, 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 (Section 7.2.2.7)
- QTcF increase > 60 msec from mean baseline measurement (pre-dose measurement on Day 1), if confirmed by cardiologist review
- Mean increase in QTcF > 30 ms from the mean baseline measurement (pre-dose measurement on Day 1). value at 1.5 hour post-dose or mean QTcF > 480 ms at Day 1 (see Section 7.2.2.7), if confirmed by cardiologist review
- Pregnancy
- Use of prohibited treatment (refer to Section 6.4.2)
- Initiation of new medical treatment for hypercortisolism due to CS
- Any other protocol deviation that results in a significant risk to the patient's safety

Patients who discontinue study treatment should NOT be considered withdrawn from the study. They should return for the assessments indicated in Table 7-2. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, email, letter) should be made to contact them as specified in Section 7.1.6.

Patients who discontinue study treatment should undergo an end of study visit and then be discontinued from the trial.

7.1.4.1 Withdrawal of informed consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent occurs only when a patient:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the patient'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.

[redacted]

Further attempts to contact the patient 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 patient's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a patient's samples until their time of withdrawal) according to applicable law.

For United States and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For European Union and RoW (Rest of World, i.e. all countries except the United States, Japan and the member states of the European Union): All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

7.1.5 Follow up for safety evaluations

All patients must have safety evaluations for 30 days after the last dose of study treatment.

Data collected should be added to the Adverse Events CRF and the Concomitant Medications

CRF. New therapies for Cushing's syndrome will be captured on the appropriate eCRF page following the last study treatment.

7.1.6 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow up should be recorded as such on the appropriate Disposition CRF.

7.2 Assessment types

7.2.1 Efficacy assessments

Efficacy assessments includes mUFC, steroid hormones, and ACTH. For steroid hormones and ACTH, please refer Section 7.2.2.4.

Table 7-4 Disease assessment collection plan

Procedure	Screening/Baseline	During Treatment/Extension
24-hour urine to test for urine free cortisol and creatinine by central lab	Mandated at screening and baseline	Mandated, at week 4, 8, 12, 24 and 48. Three 24-hour samples at each time point

[redacted]

Urinary free cortisol

The primary efficacy parameter will be urinary free cortisol (UFC) and will be assessed using a central laboratory. UFC will be measured in three 24-hour urine samples. The three samples will be averaged to obtain the mean UFC (mUFC) level.

Throughout the study, patients will collect three 24-hour UFC samples according to the Table 7-1, Table 7-2 and Table 7-3. An additional 24-hour UFC sample (unscheduled) may be collected as required by investigators.

Screening: three 24-hour UFC samples should be collected and sent to central laboratory at least 14 days prior to Day 1 in order to ensure that sufficient time is allowed for central laboratory results to become available. These samples will be used to assess eligibility of the patient. A repeated evaluation within the screening window is permitted for screening results out of the defined range. If the repeated laboratory result meets the criteria, that result may be used to determine eligibility. If the repeated laboratory result does not meet the criteria, the patient will be considered a screening failure.

Baseline: another three 24-hour UFC samples will be collected within 7 days prior to first day of treatment to serve as baseline value.

Treatment period: patient will collect three 24-hour UFC samples within 7 days prior to the next visit and with the last urine sample preferably collected the day prior to the visit at site as defined in Table 7-1, Table 7-2 and Table 7-3.

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing physical examination, vital signs, laboratory evaluations, cardiac assessments, as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 8.

7.2.2.1 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, 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 Table 7-1, Table 7-2 and Table 7-3.

Significant findings that were present prior to the signing of informed consent must be included in the Medical History page on the patient's CRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's CRF.

7.2.2.2 Vital signs

Vital signs include body temperature, blood pressure and pulse measurements, and will be assessed according to Table 7-1, Table 7-2 and Table 7-3.

After the patient has been sitting for five 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. The repeat sitting measurements will be made at 1 - 2 minute intervals and the three measurements will be reported.

[redacted]

7.2.2.3 Height, weight and waist circumference

Height in centimeters (cm) and body weight [to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes] will be measured. Body height will be measured at screening and body weight and waist circumference will be measured at visits according to Table 7-1, Table 7-2 and Table 7-3.

To measure the waist circumference, patients should remove clothing from around the waist to ensure the measuring tape is correctly positioned. Using e.g. a cosmetic pencil, make a mark at the "natural waist" midway between the palpated iliac crest and the palpated lowest rib margin in the left and right mid-axillary lines. Place the non-strechable tape evenly around the natural waist covering the left and right natural waist marks. The measurement scale should face outward, and there should be no twists in the tape. Ensure that the tape is just touching the skin but not compressing the soft tissue. Instruct patients to stand erect with abdomen relaxed, arms at sides, feet together, and weight divided equally over both legs.

7.2.2.4 Laboratory evaluations

Clinical laboratory analyses (hematology, chemistry, coagulation, urinalysis, thyroid panel and additional tests mentioned in Table 7-5 and Table 7-6 below) are to be performed by the central or local laboratory. Visit windows of +/- 3 days are allowed.

At any time during the study, abnormal laboratory parameters which are clinically significant and require an action to be taken with study treatment (e.g. require dose modification and/or interruption of study treatment, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, will be recorded on the AE CRF page. Laboratory data will be summarized using the CTCAE version 4.03. Additional laboratory evaluations are left to the discretion of the investigator.

Table 7-5 Central clinical laboratory parameters collection plan

Test Category	Test Name
Steroid hormones and ACTH	Serum testosterone and estradiol Plasma ACTH, serum cortisol, serum 11-deoxycortisol, Serum aldosterone, Serum 11-Deoxycorticosterone, [redacted]

[redacted]

Table 7-6 Local clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, WBC Morphology with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)
Chemistry	Albumin, Alkaline phosphatase, ALT (GPT), AST (GOT), Bicarbonate or pCO_2, Glucose, Calcium, Chloride, Creatinine, Creatine kinase, GGT, Lactate dehydrogenase (LDH), inorganic phosphorus, lipase, amylase, magnesium, potassium, sodium, Total Bilirubin, Direct Bilirubin, Indirect Bilirubin, Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid
Urinalysis	Macroscopic Panel (Dipstick) (Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, pH, Protein, Specific Gravity,)
Coagulation	Prothrombin time (PT) or INR, Activated partial thromboplastin time (APTT)
Thyroid Panel	Serum TSH, free T4

[redacted]

Test Category	Test Name
Additional tests	Serum cortisol Pregnancy test (serum / urine) Fasting serum insulin and HbA1C LH, FSH Serum Type I collagen cross-linked N-telopeptide (NTX) and Serum bone-specific alkaline phosphatase (BAP)

7.2.2.4.1 Hematology

Hematology tests are to be performed by the local laboratory according to the schedule of assessments and collection plan outlined respectively in Table 7-1, Table 7-2 and Table 7-3. The Hematology panel includes hematocrit, hemoglobin, platelets, red blood cells (RBC), white blood cells (WBC), WBC morphology with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils).

7.2.2.4.2 Clinical chemistry

Chemistry tests are to be performed by the local laboratory according to the schedule of assessments and collection plan outlined respectively in Table 7-1, Table 7-2 and Table 7-3. The Chemistry tests should be analyzed under the fasting condition.

The chemistry panel includes albumin, alkaline phosphatase, ALT (GPT), AST (GOT), bicarbonate or pCO_2, glucose, calcium, chloride, creatinine, creatine kinase, gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), inorganic phosphorus, lipase, amylase, magnesium, potassium, sodium, total bilirubin, direct bilirubin, indirect bilirubin, total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), total protein, triglycerides, Blood Urea Nitrogen (BUN) or urea, uric acid.

7.2.2.4.3 Urinalysis

Urinalysis tests are to be performed according to the schedule of assessments and collection plan outlined respectively in Table 7-1, Table 7-2 and Table 7-3.

A semi-quantitative "dipstick" evaluation for the following parameters will be performed: specific gravity, pH, glucose, protein, bilirubin, ketones, leukocytes esterase and blood.

7.2.2.4.4 Coagulation

Prothrombin time (PT) or INR, activated partial thromboplastin time (APTT) will be assessed by the local laboratory according to Table 7-1, Table 7-2 and Table 7-3.

7.2.2.4.5 Thyroid panel

Serum thyroid stimulating hormone (TSH) and free T4 will be assessed by the local laboratory according to Table 7-1, Table 7-2 and Table 7-3.

7.2.2.4.6 Additional hormones

Serum cortisol, luteinizing hormone (LH), and follicle stimulating hormone (FSH) will be assessed by the local laboratory according to Table 7-1, Table 7-2 and Table 7-3.

[redacted]

Serum testosterone and estradiol, plasma ACTH, serum cortisol, serum 11-deoxycortisol, serum aldosterone, [redacted] and serum 11-deoxycorticosterone will be assessed by the central laboratory according to Table 7-1, Table 7-2 and Table 7-3. Serum cortisol will be assessed by both central and local laboratories. [redacted]

7.2.2.4.7 Other laboratory parameters

Serum fasting insulin, HbA1C and bone metabolism marker [serum Type I collagen cross-linked N-telopeptide (NTX) and serum bone-specific alkaline phosphatase (BAP)] will be assessed by the local laboratory according to Table 7-1, Table 7-2 and Table 7-3.

7.2.2.4.8 Pregnancy and assessments of fertility

Serum pregnancy tests will be performed at screening and baseline. Urine or serum pregnancy testing will be performed as indicated in Table 7-1, Table 7-2 and Table 7-3.

If a urine pregnancy test is performed and is found to be positive, this will require immediate interruption of study drug until serum β-hCG is performed and found to be negative. If positive, the patient must be discontinued from the trial.

When performed at screening, the result of this test must be received before the patient may be dosed.

7.2.2.5 Radiological examinations

MRI or CT scanning will be performed only for ectopic corticotropin syndrome patient at visit according to Table 7-1, Table 7-2 and Table 7-3. If the tumor will not be detected at baseline evaluation, the following evaluations are not mandatory. The same imaging technique should be used throughout the trial, as much as possible.

The following steps should be used to assess tumors causing syndrome:

1. For baseline, imaging by using CT or MRI should be performed to confirm location of the tumors (if detectable).
2. In case of detecting tumors at baseline, locations of tumors will be recorded. The biggest tumor (i.e. tumor with the longet diameter) will be monitored for the size.
   a. The size should be captured in terms of longest perpendicular diameters.
   b. If any of the perpendicular diameters cannot be reliably measured because of its small size, the minimum limit of detection as the diameter size (e.g. 7.5 mm for CT) should be entered.
   c. A value of 0 mm X 0 mm should be entered in case of disappearance of the tumor.

The size of the tumor causing the syndrome is defined as the product of the crossdiameter of the tumor using the longest perpendicular diameters.

CT and MRI should be performed with slice thickness ≤ 7.5 mm.

7.2.2.6 Cardiac assessments

Cardiac monitoring will include 12-lead safety ECGs, which are the primary assessment of safety at study visits, and 24-hour continuous 12-lead Holter recordings, which provide large

[redacted]

amounts of additional ECG data with central reading, but are not intended to provide real-time assessment of cardiac intervals and cardiac rhythm.

Table 7-7 ECG collection plan

Week	Day	Time	ECG Type	Central or Local
-5 to -2	-35 to -8	NA	12 Lead	Local
-1	-7 to -1	NA	12 Lead	Local
-1	-7 to -1	24-hour	24-hour Holter	Central
0, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 26, 30, 34, 36, 40, 44, 48	1, 8, 15, 22, 29, 43, 57, 71, 85, 113, 141, 169, 183, 211, 239, 253, 281, 309, 337	Pre-dose and Post-dose 1.5 hours	12 Lead	Local
2, 12, 24, 48	15, 85, 169, 337	24-hour	24-hour Holter	Central
Optional Extension: 60, 72, 84, 96, 108, 120, 132, 144, subsequently with same frequency (i.e. every 12 weeks)	421, 505, 589, 673, 757, 841, 925, 1009, subsequently with same frequency	Pre-dose and Post-dose 1.5 hours	12 Lead	Local
Optional Extension: 72, 120, subsequently with same frequency (i.e. every 48 weeks)	505, 841, subsequently with same frequency	24-hour	24-hour Holter	Central
EoT: 12 [a], 48 [a], EoT	85[a], 337[a], EoT	NA	12 Lead	Local
EoT: 12 [a], 48 [a], EoT	85[a], 337[a], EoT	24-hour	24-hour Holter	Central
Follow-up	30 days from last dose	NA	12 Lead	Local
Unscheduled assessment		Anytime	12 Lead	Local
[a]: Required when patient finish the study.				

7.2.2.6.1 24-hour Holter electrocardiogram

Twenty-four hour continuous 12-lead Holter recording with central reading of data are done on each patient according to the Table 7-1, Table 7-2, Table 7-3 and Table 7-7.

7.2.2.6.2 Electrocardiogram (ECG)

Twelve-lead safety ECGs are collected at the study sites according to Table 7-1, Table 7-2, Table 7-3 and Table 7-7.

Twelve-lead safety ECGs are collected at the study site using ECG equipment provided by vendor. This ECG must be read on site by a qualified physician (e.g. the investigator or another qualified physician such as a consulting cardiologist) at the time they are collected and documented on the ECG CRF.

Each 12-lead Safety ECG tracing should be labeled with the:

- study number
- patient initials
- patient number
- date and time

[redacted]

and kept in the source documents at the study site. The clock on the ECG machine should be synchronized with the central clock on a daily basis.

The CRF will contain:

- date and time of ECG
- heart rate
- PR interval
- QT and QTcF interval
- QRS duration

The Fredericia QT formula (QTcF) to correct for variations in heart rate should be used for clinical decisions.

The purpose of the safety ECG is to identify patients with clinically significant ECG abnormalities. On the day of the first study drug administration (Day 1), pre-dose ECGs must be done in triplicate. The mean of the QTcF from these 3 tracings is used as the baseline QTcF to be compared with subsequent ECGs.

ECGs with clinically significant abnormalities should be reported on the CRF. The overall interpretation will be collected with a Yes/No statement to confirm if any clinically significant abnormalities are present which need to be specified further.

A “notable ECG abnormality” is defined as:

- Day 1 only: an increase in QTcF > 30 msec at 1.5 hours post-dose, compared to the mean pre-dose baseline QTcF from the same day. It is to eliminate subjects who experience large QT increases early and exclude them from further participation for safety.
- QTcF > 480 msec with acute cardiovascular risk, as assessed by a consulting cardiologist
- Any QTcF > 500 msec, confirmed by a consulting cardiologist
- QTcF increase > 60 msec from baseline. The 60 ms threshold at all other times excluding post 1.5 hours at Day 1 is set for the following two reasons. QTc fluctuates during normal life, and the absolute risk of Torsades des Pointes is related to the actual QTcF value (> 500 ms) and not the change from baseline.

Notable ECG abnormalities should be recorded on the Adverse Events CRF page. If there is a notable abnormality, then a cardiology consult should be called, and the Novartis medical monitor for this trial notified of the event.

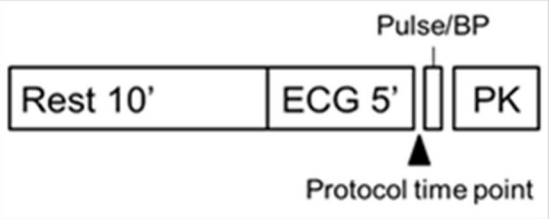
For any ECGs with clinically significant or notable ECG abnormalities, two additional 12-lead ECGs should be performed to confirm the safety finding and the triplicate ECGs collected should be transferred for central review.

ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline.

The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and then blood sampling for osilodrostat pharmacokinetic (PK) assessment (Figure 7-1). ECG procedure may also be performed 30 minutes after PK sampling.

[redacted]

Figure 7-1 Sequence of cardiovascular data collection



Original ECG tracings, appropriately signed, will be archived at study site.

7.2.2.7 QT monitoring

QT monitoring will occur as follows:

- On the first day of the first administration of osilodrostat (Day 1), pre-dose baseline ECGs must be done in triplicate. The mean of the QTcF values from these three ECG tracings is used to determine the mean baseline QTcF.
- On Day 1, if the safety ECG (1.5 hours post-first dose of osilodrostat) shows a mean increase in QTcF > 30 ms from the mean baseline value, or the mean QTcF is > 480 ms, then the patient must be discontinued from the study drug according to the discontinuation procedure described in Section 7.1.4 and an unscheduled triplicate ECGs collected at approximately 1-2 hours and a PK sample collected. The patient must remain under observation until the QTcF is < 480 msec and serum electrolytes, calcium, and magnesium are measured and the results normal.
- If at any follow up visit, a QTcF > 480 msec is observed or an increase of the QTcF of > 60 msec compared to baseline QTcF assessment, 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 patient safety, this should be initiated at the study site without delay and without waiting for confirmation by a cardiologist.

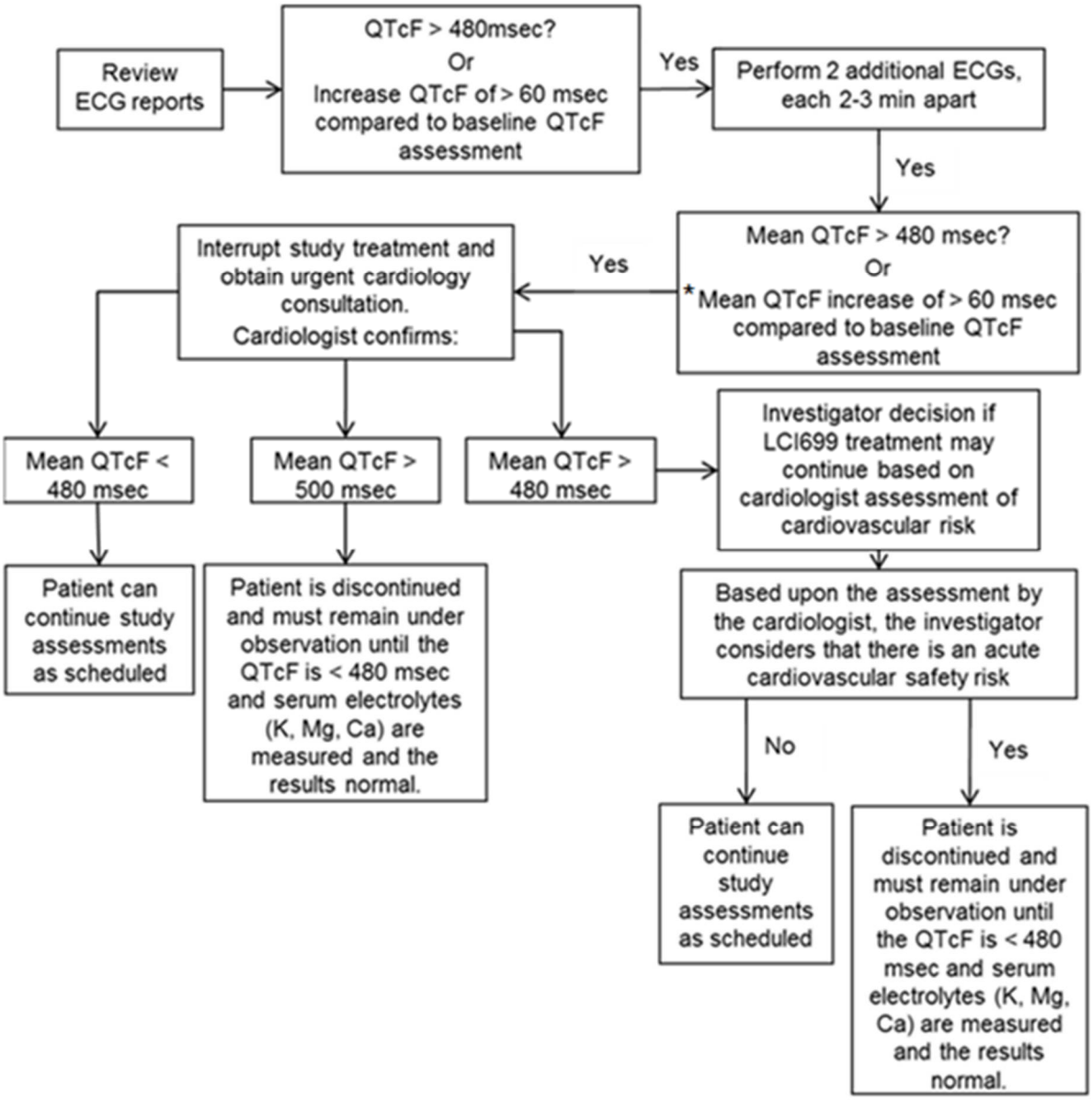
Based on the cardiologist consultation, the following should occur:

- 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 patient has to discontinue according to the discontinuation procedure described in Section 7.1.4 and an unscheduled PK sample collected. The patient 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.
  a. 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. In addition, an unscheduled PK sample will be collected.

[redacted]

b. 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 7.1.4).
c. 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 7-2 QT Monitoring Flow Chart (except for Day 1)



* Please refer to Section 7.1.4, study treatment must be discontinued under this circumstance.

[redacted]

7.2.3 Pharmacokinetics

Blood samples for osilodrostat PK evaluation will be collected from all patients who receive at least one dose of study treatment as indicated in the Visit Evaluation Schedule (Table 7-1, Table 7-2 and Table 7-3).

Time points of blood sample collection are outlined in Table 7-8.

If osilodrostat administration was interrupted prior to a planned visit and no study treatment is administered on the day of the planned visit, blood draw for PK sampling will not be required.

All ECG procedures should be taken prior to and/or 30 minutes after any PK blood draws since sampling for PK impacts ECG measurements.

Complete dosing information, including the date and time of actual blood draw and time of the last study treatment dose prior to the sampling (24-h clock time), should be obtained on all sampling days and recorded on the PK CRF and/or Contract Research Organization (CRO) requisition form(s). Sampling problems will be noted in the relevant field in the CRF.

An additional blood sample (unscheduled) should be collected in the event that a patient experiences an AE which requires premature termination from the study treatment.

[redacted]

7.2.3.1 Pharmacokinetic blood collection and handling

Refer to the [CLCI699C1201 Laboratory Manual] for detailed instructions for the collection, handling, and shipment of PK samples.

Table 7-8 Pharmacokinetic blood collection log

Week	Day	Scheduled time point [a]	Dose Reference ID	PK Sample No	Sample volume [mL]
0	1	Pre-dose/ 0 h	1	1	2.6
0	1	Post-dose 0.25 - 0.75 h	1	2	2.6
0	1	Post-dose 1 - 2 h	1	3	2.6
0	1	Post-dose 3 - 4 h	1	4	2.6
1	8	Pre-dose/ 0 h[b]	2/102	5	2.6
1	8	Post-dose 1 - 2 h	2	6	2.6
2	15	Pre-dose/ 0 h[b]	3/103	7	2.6
2	15	Post-dose 0.25 - 0.75 h	3	8	2.6
2	15	Post-dose 1 - 2 h	3	9	2.6
2	15	Post-dose 3 - 4 h	3	10	2.6
3	22	Pre-dose/ 0 h[b]	4/104	11	2.6
3	22	Post-dose 1 - 2 h	4	12	2.6
4	29	Pre-dose/ 0 h[b]	5/105	13	2.6
4	29	Post-dose 1 - 2 h	5	14	2.6
6	43	Pre-dose/ 0 h[b]	6/106	15	2.6
6	43	Post-dose 1 - 2 h	6	16	2.6
8	57	Pre-dose/ 0 h[b]	7/107	17	2.6

[redacted]

Week	Day	Scheduled time point [a]	Dose Reference ID	PK Sample No	Sample volume [mL]
8	57	Post-dose 1 - 2 h	7	18	2.6
10	71	Pre-dose/ 0 h[b]	8/108	19	2.6
10	71	Post-dose 1 - 2 h	8	20	2.6
12	85	Pre-dose / 0 h[b]	9/109	21	2.6
12	85	Post-dose 0.25 – 0.75 h	9	22	2.6
12	85	Post-dose 1 - 2 h	9	23	2.6
12	85	Post-dose 3 - 4 h	9	24	2.6
16	113	Pre-dose / 0 h[b]	10/110	25	2.6
16	113	Post-dose 1 - 2 h	10	26	2.6
20	141	Pre-dose / 0 h[b]	11/111	27	2.6
20	141	Post-dose 1 - 2 h	11	28	2.6
24	169	Pre-dose / 0 h[b]	12/112	29	2.6
24	169	Post-dose 1 - 2 h	12	30	2.6
48	337	Pre-dose / 0 h[b]	13/113	31	2.6
EoT		---	NA	1001	2.6
Unscheduled sample		---	NA	2001+	2.6

[a] The following PK assessment windows are acceptable: predose sample within 0.5 h before dose administration.
[b] For the PK predose (trough) samples, the actual date and time of administration of the previous dose of study medication should also be recorded with appropriate Dose Reference ID as indicated in the above table. The Dose Reference ID series “1, 2, 3…” is for the osilodrostat dose administered on study visit day, while Dose Reference ID series “102, 103, 104…” is for last osilodrostat dose the patient received prior to the collection of the PK predose (trough) sample.

7.2.3.2 Analytical method

The plasma samples from all patients will be assayed for osilodrostat concentrations using a validated liquid chromatography - tandem mass spectrometry assay (LC-MS/MS). The lower limit of quantitation (LLOQ) will be 0.10 ng/mL for osilodrostat; values below LLOQ will be reported as zero ng/mL, and missing samples will be labeled accordingly. Concentrations of osilodrostat will be expressed in mass per volume units (ng/mL). A further refinement of this bioanalytical method may be conducted during the course of the study.

7.2.5 Resource utilization

Not applicable

7.2.6 Patient reported outcomes

Two patient reported outcome instruments, CushingQoL and Beck Depression Inventory-II, will be used to assess the impact of treatment on patient quality of life and symptom burden (see Appendix 4). Patients must be asked to complete each questionnaire prior to clinical assessments being undertaken, and these must be completed in accordance with the schedules listed in Table 7-1, Table 7-2 and Table 7-3. Patient Questionnaires should be completed in the sequence from specific to general; CushingQoL followed by Beck Depression Inventory-II. Patient's refusal to complete all or any part of a questionnaire should be documented in the study data capture system and should not be captured as a protocol deviation. Patient questionnaires should be completed in the language most familiar to the patient. The patient should be given sufficient space and time to complete the questionnaire. The site personnel should check the questionnaire for completeness and ask the patient to complete any missing responses. The original questionnaire will be kept with the patient's file as the source document.

Completed questionnaire(s) and any unsolicited comments written by the patient should be reviewed and assessed by the investigator for responses which may indicate potential AEs or

SAEs before any clinical study examinations. This assessment should be documented in study source records. If AEs or SAEs are confirmed, study investigators should not encourage the patient to change responses reported in the completed questionnaires. Study investigators must follow reporting instructions outlined in Section 8 (e.g. reference "Adverse Events" section) of the study protocol.

7.2.6.1 CushingQoL

The Cushing's Disease Health-Related Quality of Life Questionnaire (CushingQoL) (version 1.0) that was developed to evaluate quality of life in patients with Cushing's syndrome (Webb et al. 2008). The CushingQoL is comprised of 12 items that capture patient responses on seven concepts: daily activities, healing and pain, mood and self-confidence, social concerns, physical appearance, memory and concern about the future. Content reliability, sensitivity to change and psychometric properties have been validated in patients with Cushing's disease (Nelson et al. 2013).

For this study, the CushingQoL has been modified from the standard four-week recall to a one-week recall in order to be more sensitive to the changes in patient quality of life.

7.2.6.2 BDI-II

The Beck Depression Inventory® II (BDI®-II) is a patient reported instrument that consists of 21 items designed to assess the intensity of depression in clinical and normal patients in the preceding two weeks. Each item is a list of four statements arranged in increasing severity about a particular symptom of depression.

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

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

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

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate adverse event.

[redacted]

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected though a death form.

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

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

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

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

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

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

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per

[redacted]

investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

8.1.3 Adverse events of special interest

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring may be appropriate. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest are defined on the basis of an ongoing review of the safety data. AESI are discussed in detail in the Investigator Brochure.

In addition to the AEs listed earlier (Section 1.2.1.2.2 and Section 1.2.1.2.3), other AEs are predicted by the underlying disease or the mechanism of action (MoA) of osilodrostat, specifically in patients with Cushing's disease. Many, but not all, of these AEs have been observed in preclinical and/or clinical studies.

These "AEs of Special Interest" include the following mechanistic groups:

- Adrenal Hormone Precursor Accumulation-related AEs
- Hypocortisolism related AEs
- QT-prolongation-related AEs
- Arrhythmogenic potential AEs
- Pituitary tumor enlargement related AEs

Two of the AEs of special interest, the potential for QT prolongation and hypocortisolism (glucocorticoid withdrawal/adrenal insufficiency) are described in greater detail below.

8.1.3.1 Risk of QT prolongation

Preclinical cardiac safety studies have revealed a signal of QT prolongation with osilodrostat that is consistent across *in vitro* and *in vivo* studies. The risk was quantified in an ICH E-14 compliant thorough QT/QTc study conducted in healthy volunteers (see Section 1.2.1.2.4 for a summary of the results). The results support the use of osilodrostat in doses up to 30 mg [CLCI699C2105].

8.1.3.2 Hypocortisolism (glucocorticoid withdrawal/adrenal insufficiency)

Important and closely related AEs of special interest are hypocortisolism-related adverse events including glucocorticoid withdrawal and adrenal insufficiency. These AEs are a consequence of the potent activity of osilodrostat to inhibit cortisol synthesis. In patients Cushing's disease, the relatively rapid correction of hypercortisolism can result in symptoms of glucocorticoid withdrawal. If the inhibition of cortisol synthesis is excessive, hypocortisolism-related adverse events including adrenal insufficiency may develop.

The patient should be questioned on the signs and symptoms of hypocortisolism (glucocorticoid withdrawal/adrenal insufficiency) at each visit. If any potential signs or symptoms are reported, they should be graded for severity and reported as an AE.

8.1.3.3 Definitions and reporting

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

8.2 Serious adverse events

8.2.1 Definitions

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

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

8.2.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically

[redacted]

thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site.

Follow-up information is submitted in the same way as the original SAE Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated and whether the patient continued or withdrew from study participation.

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

8.3 Pregnancies

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

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

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

8.4 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided Investigator Brochure. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

[redacted]

8.5 Data Monitoring Committee

Not applicable

8.6 Steering Committee

Not applicable

9 Data collection and management

9.1 Data confidentiality

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

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

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

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

Prior to entering key sensitive personally identifiable information (Subject Initials and exact Date of Birth), the system will prompt site to verify that this data is allowed to be collected. If the site indicates that country rules or ethics committee standards do not permit collection of these items, the system will not solicit Subject Initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the subject satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

[redacted]

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

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

9.3 Data collection

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

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

Pharmacokinetic (PK) [redacted] collected during the course of the study will be collected from the investigator sites and analyzed by Novartis or a central laboratory contracted by Novartis. The site staff designated by the investigator will enter the information required by the protocol onto the PK [redacted] Collection CRFs, as well as onto the designated CRO's requisition form. One copy of the requisition form will be sent to the CRO with the relevant information (including study number, patient ID, etc.) and one copy will be retained by the site.

ECG tracings of every Holter ECG and 12-Lead ECG if needed will be transferred to central readers. Method for data collection will be described in respective manuals. A [Laboratory Manual] will also be available for Central laboratory.

9.4 Database management and quality control

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

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

[redacted]

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

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

10 Statistical methods and data analysis

The study will be analyzed at least 2 times, at completion of study period I (Week 12), and at the final analysis after all patients complete the study. The initial analysis will be performed when all enrolled patients have completed the dose titration period of study (study period I) or have prematurely withdrawn from the study, whichever comes first. This first analysis will be the primary analysis. Additionally analyses plan to follow up patient long time safety profiles and updates.

Novartis or designated CRO will analyze all data using the SAS System for data analysis V9.3 or higher. Any data analyses carried out independently by an investigator should be submitted to Novartis before publication or presentation.

The data from all centers participating in the trial will be combined when required, so that an adequate number of patients will be available for analysis. The statistical analysis methods described in this section will focus on the analysis of the data in the first analysis of the study (study period I). Similar methods will be applied to the analyses in the extension phase as appropriate.

Given the sample size which is reflective of the rarity of this condition, data will be primarily described in individual basis except for a few endpoints including “mUFC response rate” and “Change from baseline in mUFC” and may require extra cautions in their interpretation. Details will be discussed in the statistical analysis plan (SAP).

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all enrolled patients who received at least one dose of osilodrostat. This is the default analysis set for efficacy.

10.1.2 Safety Set

The safety analysis set (SAS) includes all patients who received at least one dose of osilodrostat and had at least one valid post-baseline safety assessment.

10.1.3 Pharmacokinetic analysis set

The pharmacokinetic analysis set (PAS) consists of all patients who received at least one dose of osilodrostat and had at least one evaluable PK concentration at any visit (post-first-dose).

Additional definition of an evaluable PK blood sample will be further specified in the report and analysis plan (RAP).

[redacted]

10.2 Patient demographics/other baseline characteristics

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

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

10.3 Treatments (study treatment, concomitant therapies, compliance)

All patients will be classified into a single dose of osilodrostat for FAS, SAS and PAS.

Exposure to osilodrostat will be summarized descriptively and listed using FAS.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized by anatomical therapeutic chemical (ATC) class and preferred term for SAS.

10.4 Primary objective

The primary objective is to assess the percent change from baseline in the mean Urine Free Cortisol (mUFC) in individual patient level data at Week 12.

10.4.1 Variable

The primary endpoint is the percent change from baseline in mUFC in individual patient level data. No statistical analysis including descriptive summary will be performed for the primary analysis. Assessment of the efficacy endpoint will be based on the review of individual patient listing and figures due to very small sample size and expected variability in response caused by various patient background and disease.

The percent change will be plotted over time by individual patient. Since the Week 12 analysis will be performed when the last patient completed Week 12 assessment or discontinued earlier, data will be reported up to data cut-off point. For patients who discontinued prior to Week 12, data will not be imputed and only actual data will be provided.

10.4.2 Statistical hypothesis, model, and method of analysis

No statistical hypothesis is set up for this study.

10.4.3 Handling of missing values/censoring/discontinuations

The mUFC will be determined at a central laboratory from three 24-hour urine specimens collected within 7 days from scheduled visit date. The mean of the results from the 3 samples will be used to obtain the corresponding mUFC level for a given assessment. If a patient has two or more missing UFC values for a particular visit, the mUFC assessment for that patient at that visit will be considered missing. Otherwise, the mean of UFC samples for a given patient and timepoint will be considered as the mUFC level for that visit.

[redacted]

10.4.4 Supportive analyses

As a supportive analysis to the primary analysis, the absolute and percent change from baseline will be summarized at each visit through Week 24 for overall and by the status of prior experience of metyrapone, if applicable.

Individual patient level data of change from baseline in mUFC beyond Week 12 (e.g. Week 24, Week 48) will be plotted over time and listed in the same manner as those for the primary analysis.

10.5 Secondary objectives

There is no key secondary endpoint set up in this study. All secondary endpoints are to support individual patient response to osilodrostat.

10.5.1 Key secondary objective(s)

Not applicable

10.5.2 Other secondary efficacy objectives

Response rate (complete response rate, partial response rate and overall response rate)

Point estimates of the complete, partial and overall response rates with exact 95% confidence interval (Clopper-Pearson method) will be provided at Week 12, 24 and 48, respectively. Complete response rate is defined as the proportion of enrolled patients who has mUFC ≤ ULN. Partial response rate is defined as the proportion of enrolled patients who has mUFC > ULN and at least 50% reduction from baseline in mUFC. Overall response rate is defined as the proportion of enrolled patients who has mUFC ≤ ULN or at least 50% reduction from baseline.

Change from baseline in serum cortisol

The percent change from baseline in morning serum cortisol which will be assessed by central laboratory will be reported up for each patient over time. Additionally, descriptive summary of the absolute and the percent change will be provided at Week 12, 24 and 48.

Additionally serum cortisol will be assessed by local laboratory for dose confirmation purpose. These will be listed only.

Change from baseline in steroid hormones

Both absolute and percent change from baseline in steroid hormones in the HPA-axis will be listed over time.

Serum hormones include aldosterone, 11-deoxycorticosterone, 11-deoxycortisol, testosterone and estradiol. Plasma hormone includes ACTH.

[redacted]

Change from baseline in cardiovascular-related metabolic parameters associated with Cushing syndrome

The absolute and percent change from baseline in cardiovascular related metabolic parameters will be listed.

Parameters include fasting glucose, HbA1c, fasting lipid profile, blood pressure, body weight body mass index (BMI) and waist circumference.

10.5.3 Safety objectives

10.5.3.1 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 three mutually exclusive segments:

1. pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
2. on-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
3. post-treatment period: starting at day 30+1 after last dose of study medication

10.5.3.2 Adverse events (AEs)

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

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

Deaths and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event.

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

For each specified SEC, number and percentage of patients with at least one event part of the SEC will be reported.

10.5.3.3 Laboratory abnormalities

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

For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following summaries will be generated separately for hematology, biochemistry and urinary laboratory tests:

- frequency table for newly occurring on-treatment grades 3 or 4 (see below for details)
- listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges

Additionally, laboratory tests related to liver function will be summarized, which includes total bilirubin (TBIL), AST, ALT and alkaline phosphatase (ALP) and the combinations.

Absolute and percent change in hormones for bone metabolism will be also listed over time, which includes luteinizing hormone (LH) and follicle stimulating hormone (FSH).

10.5.3.4 Other safety data

ECG

- listing of ECG evaluations for all patients with at least one abnormality
- shift table baseline to the worst on-treatment result for overall assessments

Vital signs

Definitions of notably abnormal results have to part of the CDP, MAP, CSP and RAP.

- table with descriptive statistics at baseline, one or several post-baseline time points and percent change from baseline

10.5.3.5 Supportive analyses for secondary objectives

Not applicable

10.5.3.6 Tolerability

Tolerability will be studied in terms of dose reductions or drug interruption due to an AE.

10.5.4 Pharmacokinetics

The PAS will be used in all pharmacokinetic data analysis and summary statistics.

As sparse pharmacokinetic sampling is performed in this study, traditional non- compartmental analysis will not be performed to calculate pharmacokinetic parameters. Plasma concentration data of osilodrostat will be listed by subject, visit, incident dose and nominal sampling times. Descriptive statistics of plasma concentrations will be provided by incident dose, visit and nominal sampling times. Graphical depiction (arithmetic mean and individual) for osilodrostat concentrations over time during the course of the study will be performed by incident dose. PK data generated from this study will be used in conjunction with PK data from other clinical studies in population PK assessment. Patient demographics (e.g. age, gender, ethnicity, weight) will be explored as covariates, if appropriate. The broad principles outlined in the FDA "Guidance for Industry: Population Pharmacokinetics" will be followed during the population PK analysis. The results of population PK assessment will be presented in a separate report. [redacted] After database lock, merge PK dataset with actual elapsed time will be used for analysis.

[redacted]

10.5.4.1 Data handling principles

Plasma concentrations of osilodrostat will be expressed in ng/mL. Missing concentration values will be labeled as such in data listings. Concentrations below the lower limit of quantitation (LLOQ) will be treated as zero in summary statistics and reported as zero in data listings.

[redacted]

10.5.6 Resource utilization

Not applicable

10.5.7 Patient-reported outcomes

The CushingsQoL score is identified as the primary patient reported outcome variable of interest. Beck Depression Inventory®-II (BDI®-II) total score is identified as secondary PRO variables of interest. Missing items data in a scale will be handled based on each instrument manual. Additional details for handling missing items data will be specified in the analysis plan for instruments with no missing data handling criteria in the instrument manual.

No imputation will be applied if the total scores are missing at a visit. All available data until completion or early discontinuation during study period I and II will be listed only due to very small sample size. Details will be specified in the RAP.

[redacted]

10.7 Interim analysis

The study has no planned interim analysis for efficacy which requires consideration of multiplicity.

[redacted]

10.8 Sample size calculation

Based on medical and operational feasibility, 10 patients plan to be enrolled in this study because of the following reasons:

- According to epidemiology survey in 1997 in Japan, the incidence of CS was estimated as 1250 cases. In the 417 cases of CS which were actually reported, 35.8% had CD, 47.1% had adrenal adenoma, 17.1% had other cause of CS (Nawada et al 1999).
- Only less than 50 patients are those who need medically treatment in CS because the success rate of surgeon is very high (about 95% in adrenal adenoma can be treated by only surgery). The number of ectopic corticotropin syndrome, AIMAH and PPNAD who need medically treatment is low as well.
- Metyrapone is approved in Japan for Cushing syndrome. Therefore, some enrolled patients are expected to be inadequately controlled with metyrapone.

As a heterogeneous population will be enrolled, the effects of osilodrostat on each patient is expected to vary. Therefore, the primary analysis will be based on the percent change from baseline in mUFC at the individual patient level at Week 12.

Moreover, some of the currently planned analyses and/or data presentation may be modified if actual enrollment has not reached the original target. Detailed will be discussed in the statistical analysis plan (SAP).

10.9 Power for analysis of key secondary variables

Not applicable

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

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

11.2 Responsibilities of the investigator and IRB/IEC/REB

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

11.3 Informed consent procedures

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

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

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

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

[redacted]

11.4 Discontinuation of the study

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

11.5 Publication of study protocol and results

Novartis is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome. Novartis assures that the key design elements of this protocol will be posted on the publicly accessible database, e.g. clinicaltrials.gov before study start. In addition, results of interventional clinical trials in adult patients are posted on www.novartisclinicaltrials.com, a publicly accessible database of clinical study results within 1 year of study completion (i.e., Last patient last visit), those for interventional clinical trials involving pediatric patients within 6 months of study completion.

Novartis follows the International Committee of Medical Journal Editors (ICMJE) authorship guidelines (www.icmje.org) and other specific guidelines of the journal or congress to which the publication will be submitted.

[redacted]

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

As part of its commitment to full transparency in publications, Novartis supports the full disclosure of all funding sources for the study and publications, as well as any actual and potential conflicts of interest of financial and non-financial nature by all authors, including medical writing/editorial support, if applicable.

For the Novartis Guidelines for the Publication of Results from Novartis-sponsored Research, please refer to www.novartis.com.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

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

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. For electronic CRFs an audit trail will be maintained by the system.

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

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written

permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

11.7 Confidentiality of study documents and patient records

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

11.8 Audits and inspections

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

11.9 Financial disclosures

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

12 Protocol adherence

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

12.1 Amendments to the protocol

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

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14 Appendices

14.1 Appendix 1: Summary of Common Toxicity Criteria for Adverse Events v4.0 (CTCAE)

Table 14-1 List of summary of Common Toxicity Criteria for Adverse Events v4.3 (CTCAE)

Grade	Definition of Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
3	Severe or medically significant but not immediately life-threatening hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
4	Life-threatening consequences; urgent intervention indicated
5	Death related to AE

Activities of Daily Living (ADL)
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

[redacted]

14.2 Appendix 2: List of drugs to be used with caution with osilodrostat

Table 14-2 List of medications with potential drug-drug interactions with osilodrostat – to be used with caution

CYP1A2 substrates	CYP2C19 substrates	CYP2D6 substrates	CYP3A4/5 substrates	CYP2E1 substrates
Atypical antipsychotics: Clozapine Olanzapine **Xanthines:** Caffaine[1] Theophylline[2] **Others:** Nabumetone Riluzole Ropivacaine Zolmitriptan Alosetron[1] Duloxetine[1] Melatonin[1] Ramelteon[1] Tacrine[1] Tizanidine[1,2]	**Anti-epileptics:** Diazepam Phenytoin Phenobarbitone S-mephenytoin[1,2] **Benzodiazepines:** Clobazam[1] **Proton pump inhibitors:** Lansoprazole[1] Omeprazole[1] Pantoprazole Rabeprazole Esomeprazole **Antidepressants:** Amitriptyline Clomipramine **Others:** Clopidogrel Moclobemide Proguanil	**Antipsychotics:** Aripiprazole Chlorpromazine Clozapine Fluphenazine Haloperidol Iloperidone Pimozide Risperidone Perphenazine[1] Thioridazine[2] **Antiarrhythmics:** Encainide Flecaninide Mexilletine Prajmaline Procainamide Propafenone Sparteine Vernakalant **Alpha/Beta-adrenergic antagonists:** Metoprolol[1] Nebivolol[1] Carvedilol Propranolol Tamsulosin Timolol **Serotonin modulators:** Venlafaxine[1] Citalopram Duloxetine Fluoxetine Fluvoxamine Nefazodone Ondansetron Paroxetine Repinotan Trazodone Tropisetron **Tricyclics/ tetracyclics:** Desipramine[1] Amitriptyline Clomipramine Doxepin Imipramine Maprotiline Mianserin Mirtazapine	**Antiarrhythmics:** Quinidine[2] Dronedarone[1] **Antihistimines:** Astemizole[2] Ebastine[1] Terfenadine[1,2] **Benzodiazepines:** Brotizolam[1] Midazolam[1] Triazolam[1] Alprazolam Diazepam **Calcium channel blockers:** Felodipine[1] Nisoldipine[1] Amlodipine Diltiazem Nifedipine Nitrendipine Verapamil **Protease inhibitors:** Brecanavir[1] Capravirine[1] Darunavir[1] Indinavir[1] Lopinavir[1] Saquinavir[1] Tipranavir[1] Boceprevir Ritonavir Telaprevir **HMG CoA reductase inhibitors:** Atorvastatin[1] Lovastatin[1] Simvastatin[1] **Antibiotics:** Clarithromycin Erythromycin Telithromycin **Antipsychotics:** Aripiprazole Haloperidol Lurasidone[1] Perospirone[1] Pimozide[2] Quetiapine[1] **Immune Modulators:** Cyclosporine[2] Everolimus[1] Sirolimus[1,2]	Enflurane Halothane Isoflurane Methoxyflurane Sevoflurane Acetaminophen Chlorzoxazone Ethanol N, N-Dimethylformamide Theophylline

[redacted]

CYP1A2 substrates	CYP2C19 substrates	CYP2D6 substrates	CYP3A4/5 substrates	CYP2E1 substrates
		Nortriptyline Trimipramine **Opiods:** Codeine Dihydrocodeine Hydrocodone Methadone Oxycodone Tramadol **Others:** Atomoxetine[1] Dextromethorphan[1] Tolterodine[1] Amiflamine Brofaromine Chlorpheniramine Debrisoquine Dexfenfluramine Donepezil Fesoterodine Gefitinib Lasofoxifene Loratadine Methamphetamine Methoxyphenamine Methylphenidate Nicergolin Pactimibe Phenformin Ranolazine Ratonavir Sabeluzole Tamoxifen Traxoprodil	Tacrolimus[1,2] **Tyrosine Kinase Inhibitors:** Dasatinib[1] Neratinib[1] Imatinib Nilotinib **Opioids:** Alfentanil[1,2] Fentanyl[2] Levomethadyl[1] Methadone Others: Quinine Tamoxifen Trazodone Vincristine **Ergot derivatives:** Diergotamine/ Dihydroergotamin[2] Ergotamine[2] **Erectile dysfunction agents:** Sildenafil[1] Vardenafil[1] **Antiemetics:** Aprepitant[1] Casopitant[1] **Others:** Alpha-dihydroergocryptine[1] Aplaviroc[1] Buspirone[1] Cisapride[2] Conivaptan[1] Darifenacin[1] Eletriptan[1] Eplerenone[1] Lumefantrine[1] Maraviroc[1] Ridaforolimus[1] Ticagrelor[1] Tolvaptan[1] Vicriviroc[1]	

[1] Sensitive substrates: drugs that exhibit an AUC ratio (AUCi/AUC) of 5-fold or more when co-administered with a known potent inhibitor.
[2] Substrates with narrow therapeutic index: drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns.
This database of CYP substrates was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table; from the FDA's "Guidance for Industry, Drug Interaction Studies" and from the University of Washington's Drug Interaction Database.

[redacted]

14.3 Appendix 3: 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 osilodrostat: www.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 Novartis Medical Monitor when considering the use of medications with a "known risk to cause TdP" and with a "possible risk to cause TdP".

[redacted]

14.4 Appendix 4: Patient Quality of Life questionnaires

Cushing's Syndrome Quality Of Life Questionnaire

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

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

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

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

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

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

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

[redacted]

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

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

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

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

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

10. My illness affects my everyday activities such as working or studying.
    ☐ Always
    ☐ Often
    ☐ Sometimes
    ☐ Rarely
    ☐ Never

11. It's difficult for me to remember things.
    - ☐ Always
    - ☐ Often
    - ☐ Sometimes
    - ☐ Rarely
    - ☐ Never

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

[redacted]

Beck Depression Inventory Questionnaire

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

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

9.
- 0 I don't have any thoughts of killing myself.
- 1 I have thoughts of killing myself, but I would not carry them out.
- 2 I would like to kill myself.
- 3 I would kill myself if I had the chance.

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

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

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

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

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

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

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

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

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

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

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

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

INTERPRETING THE BECK DEPRESSION INVENTORY

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

You can evaluate your depression according to the Table below.

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

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

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