NOVARTIS

Clinical Development

LCI699 (osilodrostat)

Oncology Clinical Trial Protocol CLCI699C2302 / NCT02697734

A Phase III, multi-center, randomized, double-blind, 48 week study with an initial 12 week placebo-controlled period to evaluate the safety and efficacy of osilodrostat in patients with Cushing's disease

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List of abbreviations

ACTH	Adrenocorticotropic Hormone
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
BDI	Beck Depression Inventory
b.i.d.	*bis in diem*/twice a day
BMI	Body Mass Index
CD	Cushing's disease
CI	Confidence Interval
CMH	Cochran–Mantel–Haenszel
CNS	Central Nervous System
eCRF	Electronic Case Report/Record Form
CRO	Contract Research Organization
CS	Cushing's syndrome
CSR	Clinical study report
C-SSRS	Columbia Suicide Severity Reporting Scale
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic Blood Pressure
DHEA(S)	Dehydroepiandrosterone (Sulfate)
DMC	Data Monitoring Committee
DS&E	Drug Safety and Epidemiology
DXA	Dual-energy X-ray absorptiometry
ECG	Electrocardiogram
EDC	Electronic Data Capture
FAS	Full Analysis Set
FSH	Follicle-stimulating hormone
GFR	Glomerular Filtration Rate
eGFR	Estimated Glomerular Filtration Rate
ICH	International Conference on Harmonization
IE	Independent Endocrinologist
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
ITT	intent-to-treat
KOL	key opinion leaders
LAR	Long Acting Release
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LFT	Liver Function Test
LH	Luteinizing Hormone
LLN	Lower Limit of Normal
MoA	Mechanism of Action
MRI	Magnetic Resonance Imaging
mUFC	mean Urine Free Cortisol

PAS	Pharmacokinetic Analysis Set
PD	Pharmacodynamic
PK	Pharmacokinetic
PPS	Per-Protocol Set
PRO	Patient-Reported Outcomes
PT	Preferred Term
QoL	Quality of Life Questionnaire
QTc(F)	QT corrected (Fridericia QT formula)
eSAE	Electronic Serious Adverse Event
SAS	Safety Analysis Set
SBP	Systolic Blood Pressure
s.c.	Subcutaneous
SC	Steering Committee
SD	Standard Deviation
SEC	Safety Event Categories
SMR	standardized mortality ratio
SOP	Standard Operating Procedure
SS	Safety Set
TBIL	Total bilirubin
TdP	Torsades des Pointes
UFC	Urine Free Cortisol
ULN	Upper Limit of Normal

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient
Baseline value	Value from the last assessment prior to first dosing
Complete Response	Defined as mUFC ≤ ULN
Core phase	Includes both Period 1 and Period 2; Visits Day 1 through Week 48.
Enrollment	Point/time of patient entry into the study when informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Escape	Defined as loss of control of mUFC after week 26 (mean UFC > 1.3 x ULN on two consecutive visits on the highest tolerated dose of osilodrostat and not related to a dose interruption or dose reduction due to safety reasons) after prior mUFC normalization
Optional extension phase	Week 48 through Week 96
Study drug	Osilodrostat or placebo
Medication number	A unique identifier on the label of each blinded study drug package linked to one of the treatment groups of a study
mUFC	mUFC at a particular visit is the arithmetic mean of the urinary free cortisol (UFC) levels calculated from three 24-hour urine samples collected at screening, baseline, Week 12, Week 36, Week 48 and Week 12 follow up. The arithmetic mean of UFC from two 24-hour urine samples will be evaluated at all other study visits
Overall Response	Defined as either complete response (mUFC ≤ ULN) or partial response (mUFC > ULN with ≥ 50% reduction from baseline) during study treatment
Partial Response	Defined as mUFC > ULN with ≥ 50% reduction from baseline during study treatment
Period	Period 1: Day 1 through Week 12. Period 2: Starts immediately after the Week 12 visit through Week 48.
Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment
Subject Number (Subject No.)	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Study drug discontinuation	Point/time when patient permanently stops taking study drug for any reason
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time-points
Withdrawal of Consent	Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact

Amendment 2 (20-Dec-2019)

Amendment rationale

As of 10 December 2019, the study is fully enrolled and 45 patients are still on treatment. Of the 45 patients on treatment, 10 are active in the core phase of the study and 35 are active in the optional extension phase of the study. The last patient enrolled in the study should complete the 48 week core period by the end of Feb-2020.

The main purpose of this amendment is to change the end of study definition. After the last patient enrolled in the study completes the 48 week core period, protocol amendment 02 should be locally approved at participating sites. All remaining patients will then complete the study as soon as possible after completion of the 48 week core period, rather than after completion of the optional 48 week extension period. After local approval of this protocol amendment 02, patients who are still receiving treatment in the optional extension period (i.e. who have not yet reached week 96) will be asked to come for an end-of-treatment visit within 4 weeks after the local amendment approval date (either at their next scheduled visit if the visit is scheduled within 4 weeks after the local amendment approval, or at an unscheduled visit). Patients who are still receiving clinical benefit are eligible to join a separate long-term follow-up study.

At the time when this clinical study was set up, the optional extension phase was implemented as an initial measure to ensure that all patients benefiting from treatment during the 48 week core period would have a possibility to continue receiving treatment, and to ensure that emerging safety and efficacy data would be captured. As of the date of release of this amendment, a separate long-term follow-up study collecting long term efficacy and safety data is now open at all sites with ongoing patients. This provides a means for long-term safety and efficacy data to be collected within a prospective clinical trial setting for all eligible patients, without impacting the primary and key secondary objective of this study.

Other changes include:

- The Beck Depression Inventory (BDI) was removed from Appendix 3 as BDI is not used in the study. For this study, the BDI-II is used
- Appendix 3, Patient Quality of Life questionnaires, deleted for version control.

Changes to the protocol

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

- List of abbreviations: the list of abbreviations was updated
- Protocol Summary table, study design updated language to remove duration of 48 week Extension phase.
- Protocol Summary table study design: updated to add additional parameters to be blinded in period 1; urine creatinine, aldosterone, renin, estradiol, estrone, androgens (testosterone, delta-4 androstenedione, DHEAS), and precursors 11-deoxycortisol, 11-deoxycorticosterone

- Protocol Summary table, extension phase: defined as optional open label Extension phase and patients must end participation in the optional Extension phase within 4 weeks after Protocol Amendment 02 is approved at the site, or by Week 96, whichever occurs first
- Section 1.1.1: Corrected reference from 'Amaldi, et al 2003' to 'Arnaldi, et al 2003'
- Section 2.2.4 Optional Extension Phase: updated section title to 'Optional extension phase' and language added to clarify per Protocol Amendment 02 ongoing patients must end participation in the optional extension period within 4 weeks after Protocol Amendment 02 is approved at the site or by Week 96, whichever occurs first
- Section 2.2.6 ECG Monitoring: language added to clarify Holter recordings to be performed as applicable at Week 72, and at the end of treatment visit in the optional Extension phase.
- Section 4.1. Description of study design: deleted language defining optional extension period as 48 weeks
- Section 4.1 Description of study design: updated to add additional parameters to be blinded in period 1; urine creatinine, renin, estradiol, estrone, androgens (testosterone, delta-4 androstenedione, DHEAS), precursors 11-deoxycortisol, 11- deoxycorticosterone.
- Section 4.1 Description of study design: Extension phase updated to clarify patients enrolled in the optional extension period must end study participation within 4 weeks after Protocol Amendment 02 is approved at the site or by Week 96, whichever occurs first. Patients who are benefitting from study treatment, have the option to enter a separate long-term safety follow-up study or stop study treatment. Patients who do not enter the long-term safety follow-up study will discontinue osilodrostat and conclude the study with a Post-Treatment (End of Study) visit after 30 days off study drug
- Section 4.1 Description of study design: Clarified that during the extension phase the dose of osilodrostat will be maintained at the established effective dose unless a change is required based on mUFC results collected at Weeks 48, and if applicable, at Weeks 60, 72, and 84
- Section 4.3 Definition of end of the study: updated and clarifiedcompletion of the study as a whole (last patient last visit) will occur once all patients have completed all assessments as per Table 7-1a, Table 7-1b (Core) and, as applicable, Table 7-2 (optional Extension), or have discontinued from the study, including Post-treatment follow-up or transition into the long-term safety follow-up study, whichever occurs first, and patients end participation in the optional extension period within 4 weeks after Protocol Amendment 02 is approved at the site, or by Week 96, whichever occurs first
- Section 6.1.5 Treatment duration: updated to clarify the optional extension phase will end when all patients who were eligible, have transitioned into the long-term safety follow-up study, or were discontinued from the study. Patients must end participation in the optional extension phase within 4 weeks after Protocol Amendment 02 is approved at the site, or by Week 96, whichever occurs first. Patients participating in the optional extension phase between Week 48 and Week 72, and who are eligible, should transition into the long-term safety follow-up study at the next study visit. Patients participating in the optional extension phase between Week 72 and Week 96, and who are eligible, should transition into the long-term safety follow-up study within 4 weeks, at an unscheduled visit, of Protocol Amendment 02 approval at the site.

- Section 6.2.3 Extension phase (weeks 48-96): changed Week 96 to optional extension phase, removed separate long-term safety follow-up study from option b, and updated and clarified patients must end participation in the optional extension phase within 4 weeks after Protocol Amendment 02 is approved at the site, or by Week 96, whichever occurs first
- Section 6.5.3 Treatment blinding: updated to add additional parameters to be blinded in period 1; urine creatinine, renin, estradiol, estrone, androgens (testosterone, delta-4 androstenedione, DHEAS), precursors 11-deoxycortisol, 11- deoxycorticosterone.
- Section 7.1 Study flow and visit schedule: added language to clarify patients must end participation in the optional extension period within 4 weeks after Protocol Amendment 02 is approved at the site, or by Week 96, whichever occurs first
- Section 7.1.3 Treatment phase: clarified at Week 48, patients have the option to enter an optional open-label extension phase; however; patients currently enrolled in the optional Extension phase must end study participation within 4 weeks after Protocol Amendment 02 is approved at the site, or by Week 96 whichever occurs first. If patients are benefitting from study treatment, they have the option to enter a separate long-term safety follow-up study or stop study treatment. Patients not entering the long-term safety follow-up study will complete the study with a 30 day follow-up.
- Section 7.1.4 Discontinuation of Study drug: removed Week 96
- Table 7-3 Disease and Imaging Assessment collection plan: added language for clarification, DXA scan mandated at End of Treatment Core and End of Treatment Extension, unless EOT occurs less than 6 months before the scheduled Week 96 visit.
- Section 7.2.1.3 Bone mineral density assessments: clarified if EOT occurs less than 6 months before the scheduled Week 96 visit, MRI (or CT) and DXA is not mandatory at EOT
- Section 7.2.2.5 Radiological examinations: clarified if EOT occurs less than 6 months before the scheduled Week 96 visit, MRI (or CT) and DXA is not mandatory at EOT
- Table 7-6 ECG collection plan: added language for clarification, Patients end participation in the optional extension period study within 4 weeks after Protocol Amendment 02 is approved at the site, or by Week 96, whichever occurs first
- Section 7.2.2.6.1 24-hour Holter Electrocardiogram: Patients should be instructed to return their 24-hour Holter flashcards to the site at their next study visit in order to facilitate timely central reading of the Holter data
- Table 7-10 Hair Cortisol sample collection plan: clarified extension phase is optional and added language Patients to end study participation once Protocol Amendment 02 is approved at the site, or by Week 96, whichever occurs first
- Section 7.2.6 Patient reported outcomes: removed reference for Appendix 3
- Table 7-11 Patient reported outcomes (PROs) collection plan: added language for clarification, Patients to end study participation within 4 weeks after Protocol Amendment 02 is approved at the site, or by Week 96, whichever occurs first
- Section 10: Removed text stating that the results and outcomes of primary analysis will be presented in a CSR

- Section 10.5.2.2 Assess the change in mUFC during the Core and Extension periods of the study: updated the section title to optional Extension periods
- Section 10.5.3.4 Other safety data: updated to clarify that tumor invasiveness is also evaluated
- Reference: FDA Guidance for Industry Suicidality corrected from 2015 to 2010 to match protocol referenced in Section 10.5.3.4 under the Columbia Suicide Severity Reporting Scale (C-SSRS)
- Reference: added Masri-Iraqi et al, 2014 to match reference in Section 2.6
- Clarifications were made in the protocol that extension phase is an optional extension phase

IRBs/IECs

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

The changes described in this amended protocol 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 (20-Nov-2017)

Amendment rationale

As of 20 Nov 2017, 18 patients have been enrolled (treated) in the study.

The main purpose of this amendment is to align the language of all ongoing studies in Cushing's disease indication for prohibited drugs due to TdP risk and to add a statement regarding the risk of neutropenia observed in LCI699C2201 and LCI699C2103. These were newly acquired information added to the Investigator's Brochure for transparency, and are thus being added to all protocols. New objectives and endpoints on cortisol biomarkers were added to maintain consistency between the protocol and data collection occurring in the study, as described in the VES.

The duration of the optional extension period was increased in order to collect additional 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 study is set up at participating sites. Based on this extension, the end of study definition has been updated.

This protocol amendment introduces the following changes:

- 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.
- Addition of the following secondary objective and endpoint to ensure that analyses related to changes in other biomarkers of hypercortisolism is part of the protocol. These other markers are important to describe changes in disease burden following treatment.
    - Objective: To assess the change from baseline in serum, salivary and hair cortisol levels during the Core and Extension periods of the study.
    - Endpoint: Actual and percentage change in biomarkers of hypercortisolism (serum cortisol, late night salivary cortisol, morning cortisol and hair cortisol) from baseline to each post-baseline visit during the Core and Extension at which cortisol biomarkers are collected by treatment arms and for all patients.
- Language added to clarify that the study will end once all patients have completed all assessments as per Table 7-1a and Table 7-1b (Core) and Week 96 visit (extension phase) or have discontinued from the study early, whichever occurs first. In addition, visits are added for patients who continue to benefit from treatment at Week 96 to continue treatment on study until any of the following occurs:

  (a) they no longer benefit from treatment or

(b) a separate long-term safety follow-up study or managed access program becomes locally available or

(c) an alternative treatment option becomes locally available or

(d) all patients have either reached Week 96 or have discontinued from the study before Week 96.

- Specifying sample collection requirement in the event of suspected hypocortisolism or adrenal insufficiency during period 1 to allow dose modification by Independent Endocrinologist (IE).
- Specifying that the screening Thyroid Panel, FSH, and Pregnancy (serum) tests should be done post wash out during screening period.
- Columbia Suicide Severity Rating Scale (CSSRS) was removed from Appendix 3 as paper CSSRS is not used in the study (electronic version is used in the study)
- Introduced more flexible wording regarding the description of osilodrostat tablet strengths used in the study.
- The tumor aggressiveness evaluation was added to evaluate the prevalence of tumors with extension outside sella turcica and/or invasion into surrounding structures at baseline and during the study (new onset/disappearance).

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 2.2.6: updated to clarify that the 24-hour continuous 12-lead Holter recordings will be performed at baseline, Weeks 2, 12, 14, 36, 72, and at the end of treatment Extension visit.
- Section 2.6: updated to include the possibility of neutropenia based on observed cases with osilodrostat.
- Section 3, Table 3-1, and Section 10.5.2.8: addition of the following secondary objective and endpoint:

Objective: To assess the change from baseline in serum, salivary and hair cortisol levels.

Endpoint: The actual and percentage change from baseline in serum cortisol, late night salivary cortisol, morning salivary cortisol and hair cortisol levels for every visit in the Core and extension phases at which the biomarkers of hypercortisolism are collected, by treatment arms and for all patients.

- Section 4.1: added the following statement: Three 24-hr UFC urine samples and two late night salivary cortisol samples are to be collected after completion of the washout period during screening to assess study eligibility.
- Section 4.3: Clarified definition of end of the study
- Section 6.2.3: added the following statement:

Patients who continue to benefit from treatment at Week 96 have the option to continue treatment on study until any of the following occurs:

(a) they no longer benefit from treatment or
(b) a separate long-term safety follow-up study or managed access program becomes locally available or
(c) an alternative treatment option becomes locally available or
(d) all patients have either reached Week 96 or have discontinued from the study before Week 96,

For patients who transition into a separate long-term study or managed access program, the EOS (last dose + 30 days) visit is not applicable, as treatment on osilodrostat will not be interrupted, and only the EOT visit will be performed.

Those patients who will not continue treatment will complete the EOT extension visit and an EOS (last dose + 30 days) visit, for details of assessments, please refer to Section 7.1.4.

- Section 6.3.1, Table 6-1, the following statement is added:

The IE can adjust the dose when sufficient information is provided, i.e., serum cortisol, one or more (up to three) 24-hour UFC result, plasma glucose and electrolytes, (as central lab assessment) and completed eCRF pages with clinical signs and symptoms associated with hypocortisolism/adrenal insufficiency event.

- Section 6.3.1, Table 6-2, included discontinuation requirement when Isolated AST or ALT elevation is > 10.0 - 20.0 x ULN: If not resolved after 4 weeks, discontinue from study drug
- Section 6.3.2: added the following statement:

In the event of suspected hypocortisolism or adrenal insufficiency during period 1, the site should instruct the patient to collect one or more (up to three) 24-hour urine samples for UFC assessment and come to the site for tests for serum cortisol, plasma glucose and electrolytes (sodium and potassium). These samples should be sent to central laboratory immediately to allow an appropriate dose modification by IE. Physical exam is recommended and a record of abnormal findings should be annotated in the CRF.

- Section 6.4.3, Section 6.4.3.1, and Appendix 2: revised to update the QT-specific concomitant medication guidance for osilodrostat 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, according to (CredibleMeds®).
- Table 7-1a: Specifying that the screening Thyroid Panel, FSH, and Pregnancy (serum) tests should be done post wash out during the screening.
- Table 7-2, Table 7-6, [redacted] and Table 7-11: Additional visits are added for patients who continue to benefit from treatment at Week 96 to continue treatment on study until any of the following occurs:

(a) they no longer benefit from treatment or
(b) a separate long-term safety follow-up study or managed access program becomes locally available or
(c) an alternative treatment option becomes locally available or
(d) all patients have either reached Week 96 or have discontinued from the study before Week 96.

- Section 7.1.4, amending that hypertension should be defined as office mean supine systolic BP > 180 mmHg or mean supine diastolic BP > 110 mmHg (confirmed and persistent*).
- Table 7-7: updated the blood volume to approximately 3mL and the following footnote:

pre-dose sample within 0.5 h before dose administration, ±10 min for up to the 2 h timepoint, and within 0.5h before the 12h post dose sampling. If patient enters the extension phase of study, the 12 h post dose sampling should be taken prior to the first dose in the extension phase

- Section 10.5.2.8: added the following statement:

Change in the actual and percentage change from baseline to each post-baseline visit for serum cortisol, late night salivary cortisol, morning salivary cortisol and hair cortisol levels will be assessed. Descriptive summaries will be provided for every visit in the Core and Extension phases at which the biomarkers of hypercortisolism are collected. Salivary cortisol samples will only be included if they are collected within the correct time window. 95% CIs for the percentage change from baseline will also be provided by treatment and for overall patients.• Section 10.5.3.4: added the following statement: The tumor aggressiveness is also evaluated, in terms of the prevalence of tumors with extension outside sella turcica and/or invasion into surrounding structures at baseline and during the study (new onset/disappearance).

- Language "(depending on availability)" was added in front of all text mentioning 20 mg tablet strength.
- Appendix 3: Columbia Suicide Severity Rating Scale (CSSRS) was removed.
- Editorial changes and clarifications were made at various places in the protocol.

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.

Protocol summary:

Protocol number	CLCI699C2302
Title	A Phase III, multi-center, randomized, double-blind, 48 week study with an initial 12 week placebo-controlled period to evaluate the safety and efficacy of osilodrostat in patients with Cushing's disease
Brief title	Efficacy and safety evaluation of osilodrostat in Cushing's disease
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The study aims to confirm efficacy and safety of osilodrostat for the treatment of patients with Cushing's disease (CD) who are candidates for medical therapy.
Primary Objective(s) and Key Secondary Objective	Primary: To demonstrate the superiority of osilodrostat compared to placebo in achieving a complete response (mUFC ≤ ULN) at Week 12. Key secondary: To assess the complete response rate in both arms combined at Week 36 in patients receiving osilodrostat treatment.
Secondary Objectives	To assess the proportion of patients with a complete response (mUFC ≤ ULN) or a partial response (mUFC decrease ≥50% from baseline and >ULN) at Week 12, Week 36, and Week 48. To assess the change in mUFC during the Core and Extension periods of the study. (Refer to Table 7-1a, Table 7-1b and Table 7-2 for the study visit and evaluation schedule during the Core and Extension phases, respectively). To compare the time-to-first control of mUFC during the placebo-controlled period (Weeks 1-12) between the randomized treatment arms. To assess the time-to-escape during osilodrostat treatment up to Week 48. To assess cardiovascular and metabolic related parameters associated with CD (fasting plasma glucose, HbA1c, fasting lipid profile, blood pressure, weight and waist circumference) by assessing actual and percent change from baseline and shift table at Weeks 12, 36, and 48. To assess the change from baseline at Weeks 12, 36, and 48 in physical features of CD. To assess the change from baseline in bone mineral density (BMD) by DXA scan at the lumbar spine and total hip at Week 48. To determine the safety and tolerability of osilodrostat in the study population. To assess the change from baseline in Health Related Quality of Life, as measured by the CD-specific QoL questionnaire (CushingQoL); by the Beck Depression Inventory (BDI-II); and by the general health-related QoL instrument EQ-5D-5L, by randomized treatment arm and overall. To evaluate pharmacokinetic exposure of osilodrostat in the study population. To assess the change in cortisol levels (serum cortisol, late night salivary cortisol, morning cortisol and hair cortisol) during the Core and Extension periods of the study.
Study design	This is a Phase III, global, multi-center, randomized, double-blind, placebo-controlled study. The study design is placebo-controlled during the first 12 weeks, followed by open-label treatment with osilodrostat until week 48, and an optional Extension phase. **Screening (up to 8 weeks):** Written informed consent must be obtained before any study specific assessments. Washout of current drug therapy for CD, as well as optimization of treatment of co-morbidities is to be completed. Three 24-hr UFC urine samples and two late night salivary cortisol samples are to be collected after completion of the washout period to assess study eligibility. Other assessments needed for eligibility are detailed in Table 7-1a.

	Core Phase **Period 1 (Weeks 1-12) Double-blind, placebo-controlled:** Study visits are performed at Day 1, Week 2, Week 5, Week 8 and Week 12. The initial dose of study drug (osilodrostat or placebo) is 2 mg b.i.d. The mean of three 24-hr UFC values (mUFC) will be done at screening (prior to Period 1), baseline and Week 12. The mean of two 24-hr UFC values (mUFC) is the basis for dose titration decisions (See Section 6.2 for details). If the mUFC remains >ULN, dose escalation needs to occur according to the following sequence: 5 mg b.i.d., 10 mg b.i.d., and 20 mg b.i.d at Weeks 2, 5, or 8, as applicable. Dose escalation stops when the mUFC is ≤ ULN. Doses may be down titrated in both the active control and placebo arms (to the previous dose, or to below 2 mg b.i.d.) if mUFC is below the LLN or close to the lower limit of the normal range and/or the patient has signs or symptoms of adrenal insufficiency. Down-titration to doses less than 2 mg b.i.d. (with mock down-titration in the placebo arm to maintain the treatment blind) could also be used (Section 6.2.1 for further details). Intermediate doses may only be used in specific circumstances (see Section 6.2.1.3 for details). Dose adjustments will be done between study visits to allow the next UFC assessment to reflect the impact of the new dose of study drug (see Sections 4.1). In patients discontinuing study drug before Week 12, every effort should be made to continue visits and assessments up to and including Week 12 (see Section 4.1). To maintain the treatment blind, the UFC, urine creatinine, serum and salivary cortisol, Adrenocorticotropic Hormone (ACTH), aldosterone, renin, estradiol, estrone, androgens (testosterone, delta-4 androstenedione, DHEAS), and precursors 11-deoxycortisol, 11-deoxycorticosterone will be kept blinded to patients, investigators and the Novartis Clinical Trial Team during Period 1 (see Section 6.5.3). A group of independent endocrinologists (IEs) is responsible for managing dose titrations during this period. The IE will have access to relevant data including UFC, serum cortisol, ACTH and chemistry results, the treatment assignment, and clinical signs and symptoms at the most recent study visit. The IE is responsible for determining the dose of study drug as soon as the mUFC results are available for individual patients. The IE communicates instructions regarding the dose of study drug in a blinded manner via Interactive Response Technology (IRT) to the appropriate site. **Period 2 (Weeks 12-48): Open-label treatment:** All patients receive active, open label drug, osilodrostat, during Period 2. Immediately after the Week 12 visit, all patients that were receiving doses of 2 mg b.i.d. or above, regardless of treatment assignment (active drug or placebo) during Period 1, will receive osilodrostat 2 mg b.i.d. Patients treated with either osilodrostat or matching placebo at doses less than 2 mg b.i.d. during Period 1 will receive open label osilodrostat at the same dose. As in Period 1, dose escalation in Period 2 will be based on mUFC results (mUFC > ULN). All dose adjustments will be made by the investigator who will have access to mUFC and all other lab values from Week 14 onwards. The IE does not participate in dose decisions beyond Week 12. The investigator should be vigilant for signs or symptoms of adrenal insufficiency or glucocorticoid withdrawal between Week 12 and the receipt of Week 14 UFC results, and may reduce or temporarily withhold osilodrostat if clinically indicated. The dose escalation sequence in all patients in Period 2, regardless of Period 2 starting dose (either 2 mg b.i.d. or doses less than 2 mg b.i.d.), is 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 (see Section 6.2.2). During Period 2, three 24-hr UFC values will be used to calculate mUFC at Week 36 and Week 48; the mean of two 24-hr UFC values will be calculated at all other visits to inform dose titrations. A patient is considered to have reached a stable efficacious dose when, mUFC remains ≤ ULN. The dose may be up-titrated for mUFC > ULN, or down-titrated for mUFC values <LLN or close to the lower limit of the normal range and/or if the patient has signs or symptoms of adrenal insufficiency. Intermediate doses

	may be used only in specific circumstances. Please see Section 6.2.1.3 for details. **Optional Extension phase (Weeks 48-96):** At Week 48, patients have the option to enter an optional open-label Extension phase. Patients must end participation in the optional Extension phase within 4 weeks after Protocol Amendment 02 is approved at the site, or by Week 96, whichever occurs first. Doses can be adjusted in this phase of the study as described above and in Section 6.2.3
Population	The study population will be comprised of approximately 69 adult male and female patients with Cushing's disease who are candidates for medical therapy (see Section 5.1).
Inclusion criteria	Key inclusion criteria are listed below; please refer to Section 5.2 for the full list of inclusion criteria. • Confirmed CD that is persistent or recurrent as evidenced by all of the following criteria being met (i.e., a, b and c): a. mUFC > 1.3 x ULN (Mean of three 24-hour urine samples collected preferably on 3 consecutive days, during screening after washout of prior medical therapy for CD (if applicable), confirmed by the central laboratory and available before Day 1), with ≥2 of the individual UFC values being > 1.3 x ULN. b. Morning plasma ACTH above Lower Limit of Normal c. Confirmation (based on medical history) of pituitary source of excess ACTH as defined by any one or more of the following three criteria: i. Histopathologic confirmation of an ACTH-staining adenoma in patients who have had prior pituitary surgery. OR ii. MRI confirmation of pituitary adenoma > 6 mm OR iii. Bilateral inferior petrosal sinus sampling (BIPSS) with either CRH or DDAVP stimulation for patients with a tumor ≤ 6mm. The criteria for a confirmatory BIPSS test are any of the following: • Pre-dose central to peripheral ACTH gradient > 2; • Post-dose central to peripheral ACTH gradient > 3 after either CRH or DDAVP stimulation • Patients that received glucocorticoid replacement therapy must have discontinued such therapy for at least seven days or 5 half-lives prior to screening, whichever is longer. • Patients with *de novo* CD can be included only if they are not considered candidates for surgery (e.g., poor surgical candidates due to co-morbidities, inoperable tumors, patients who refuse to have surgical treatment, or surgical treatment is not available). • For patients with a history of pituitary irradiation: at least 2 years for stereotactic radiosurgery (SRS), and 3 years for conventional (fractionated) radiation, respectively, must have elapsed from the time of the most recent radiation treatment to the time of enrollment into this study. • Washout of any current drug therapy for CD. The following minimum washout periods must be completed before baseline efficacy assessments are performed: a. Steroidogenesis inhibitors (ketoconazole, metyrapone): 1 week b. Pasireotide s.c. (immediate release formulation): 1 week c. Mifepristone: 3 weeks d. Dopamine agonists (e.g., cabergoline), or PPAR-gamma agonists (e.g., rosiglitazone, pioglitazone): 4 weeks

	e. Pasireotide LAR: 8 weeks. Rescreening can be used as needed to ensure washout is complete. f. Mitotane: 6 months. Rescreening can be used as needed to ensure washout is complete.
Exclusion criteria	Key exclusion criteria are listed below; please refer to Section 5.3 for the full list of exclusion criteria. • Patients with pseudo-Cushing's syndrome. This may be diagnosed by two normal late night salivary cortisol values collected during the screening period and after washout of prior CD medication. • Patients with risk factors for QTc prolongation or Torsade 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; concomitant medications known to prolong the QT interval; patients with hypokalemia, hypocalcaemia, or hypomagnesaemia, if not corrected before pre-dose Day 1. • Patients likely to require adrenalectomy, pituitary surgery, or radiation therapy during the placebo-controlled period (Weeks 1-12) for the treatment of severe hypercortisolism or pituitary tumor growth causing compression of the optic chiasm. • Patients with compression of the optic chiasm due to a macroadenoma or patients at high risk of compression of the optic chiasm (tumor within 2 mm of optic chiasm). • Patients who have a known inherited syndrome as the cause for hormone over secretion (i.e. Carney Complex, McCune-Albright syndrome, MEN-1, AIP). • Patients with Cushing's syndrome due to ectopic ACTH secretion or ACTH-independent (adrenal) Cushing's syndrome. • Patients who have undergone any major surgery within 1 month, or undergone transsphenoidal pituitary surgery within 3 months, prior to screening. • Hypertensive patients with uncontrolled blood pressure defined as SBP > 180 and/or DBP > 105 or not optimally treated for hypertension as judged by the investigator. • Diabetic patients with poorly controlled diabetes as evidenced by HbA1c > 9 % or not optimally treated for diabetes mellitus as judged by the investigator. • Patients who are not euthyroid as judged by the investigator. • Patients with liver disease such as cirrhosis, chronic active hepatitis, or chronic persistent hepatitis, or patients with serum ALT and/or AST > 3 x ULN, or total bilirubin > 1.5 x ULN. Please refer to Section 5.2 and Section 5.3 for the full list of study inclusion and exclusion criteria, respectively.
Investigational and reference therapy	Osilodrostat 1 mg, 5 mg, 10 mg and (depending on availability) 20 mg film-coated tablets, and matching placebo film-coated tablets, for oral administration. Each tablet strength is provided in a separate bottle.
Efficacy assessments	24-hour Urine Free Cortisol for the primary and key secondary endpoints. Other assessments for secondary endpoints include: weight, waist circumference, blood pressure, fasting plasma glucose, HbA1c, fasting lipid profile, Health-related Quality of Life questionnaires (CushingQoL, Beck Depression Inventory-II, and EQ-5D-5L), physical features of Cushing's disease, biomarkers of hypercortisolism, BMD at lumbar spine and total hip (by DXA).
Safety assessments	Adverse events Laboratory evaluations (chemistry, hematology, coagulation, Thyroid Panel, FSH, LH, fasting plasma glucose, urinalysis and pregnancy test); ECG, Holter recordings, MRI of pituitary, vital signs, physical exam and C-SSRS.

Data analysis	The primary efficacy variable is the proportion of randomized patients in each treatment arm that are complete responders at Week 12. A complete responder is defined as a patient who has mUFC ≤ ULN (based on central laboratory result) at Week 12. The primary analysis will be based on a Cochran–Mantel–Haenszel (CMH) exact test stratified by the history of pituitary irradiation (yes/no) using the FAS. Following the ITT principle, patients are analyzed according to the drug and stratum they were assigned to at randomization. The statistical null hypothesis states that the complete response rates at the end of the 12-week placebo-controlled period (i.e., at Week 12) are the same between the two randomized arms. If the 1-sided p-value is ≤ 0.025, and the odds ratio (osilodrostat vs. placebo) is > 1, the null hypothesis will be rejected and the complete response rate in the osilodrostat arm is considered higher than that in the placebo arm. The key secondary objective is to assess the complete response rate (proportion of patients with mUFC ≤ ULN) in both arms combined at Week 36 in patients receiving osilodrostat treatment, i.e., patients randomized to placebo who do not switch to osilodrostat will not be included. In this analysis, patients with missing mUFC assessments at Week 36 will be considered as non-responders. For the key secondary objective, the statistical null hypothesis states that the complete response rate at Week 36 is < 30%. The analysis of the key secondary objective will be based on the 2-sided 95% exact confidence interval (CI) constructed using the Clopper-Pearson method in FAS patients receiving osilodrostat treatment. If the lower bound of this 95% confidence interval is ≥ 30%, the null hypothesis will be rejected and the complete response rate will be considered at least 30% at Week 36. The above testing on the key secondary objective will only be carried out if the null hypothesis for the primary objective is rejected. This sequential procedure will ensure preservation of the overall 2-sided type 1 error at 5%. The analysis of the key secondary endpoint will be performed in FAS patients receiving osilodrostat treatment and will be repeated using PPS patients receiving osilodrostat treatment as supportive analysis. In addition, the key secondary endpoint will also be analyzed using the patients randomized to the osilodrostat arm only.
Key words	Cushing's disease, LCI699, osilodrostat, Pituitary Gland, Adrenocorticotropic Hormone, ACTH, UFC

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

1.1.1 Epidemiology and pathogenesis of Cushing's syndrome and Cushing's disease

Endogenous Cushing's syndrome (CS) is rare (estimated prevalence of less than 1 in 10,000 inhabitants) (Feelders, et al 2012). The causes of endogenous Cushing's syndrome are classified into ACTH-dependent and ACTH-independent etiologies. The most common cause of Cushing's syndrome is Cushing's disease (CD), which occurs in about 70% of cases, and is due to an ACTH-secreting pituitary corticotroph adenoma. Cushing's disease most commonly affects adults aged 20-50 years, with a marked female preponderance. The other main cause of ACTH-dependent Cushing's syndrome is ectopic ACTH secretion from non-pituitary tumors (e.g., small cell lung cancer). The ACTH-independent etiologies of Cushing's syndrome are adrenal diseases such as adrenal tumors (adenomas or carcinomas) or bilateral adrenal hyperplasia.

Endogenous Cushing's syndrome is characterized by chronic hypercortisolism, which results in a variety of metabolic abnormalities and co-morbidities that collectively lead to an overall 4-fold higher mortality rate than age- and gender-matched subjects in the general population (Arnaldi, et al 2003). The increased cardiovascular risk is related to the following clinical manifestations of Cushing's syndrome: metabolic syndrome, insulin resistance, visceral obesity, glucose intolerance, hypertension, dyslipidemia, and hypercoagulation. Other clinical signs and symptoms of Cushing's Syndrome 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 in both gender, and menstrual disorders in women (Newell-Price, et al 2006).

At the time of diagnosis of Cushing's disease, the prevalence of co-morbidities has been reported as follows: 58–85% of patients have hypertension, 32–41% have obesity, 20–47% have diabetes mellitus, 50–81% have major depression, 31–50% have osteoporosis, and 38–71% have dyslipidemia (Feelders, et al 2012).

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

However, mortality studies have consistently shown that the mortality rate is significantly impacted by the biochemical status of the disease, i.e., persistent/recurrent hypercortisolism compared to biochemical remission of the disease. A recent meta-analysis of published mortality studies (Clayton, et al 2011) showed that the standardized mortality ratio (SMR) is

much higher in Cushing's disease patients with persistent hypercortisolism (SMR=5.5) than those in remission (SMR=1.2).

1.1.2 Current treatment modalities

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

The treatment options for CD include pituitary surgery, pituitary irradiation, medical therapy and bilateral adrenalectomy. The primary treatment is surgical removal of the pituitary tumor via transsphenoidal resection with the intention of cure. Second-line treatments include: more radical pituitary surgery (re-operation), radiation therapy, medical therapy, and bilateral adrenalectomy. This categorization of primary and secondary therapies reflects the International Consensus Statement prepared by 32 academic experts from 9 countries (Biller, et al 2008).

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

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

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

Pasireotide (Signifor®), a second generation somatostatin analogue, is currently approved in the US and in EU for the treatment of Cushing's disease. In the pivotal phase 3 trial, pasireotide was effective in normalizing or reducing by > 50% urinary free cortisol in 34% to 41% of patients, in study groups randomized to 0.6 mg s.c. b.i.d. and 0.9 mg s.c. b.i.d., respectively.

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

Several other drugs have been used with or without regulatory approval for the treatment of Cushing's disease, including: ketoconazole and metyrapone (steroidogenesis inhibitors), mitotane (adrenolytic agent), and cabergoline (dopamine agonist).

Bilateral adrenalectomy is deferred until all other options have been exhausted (Biller, et al 2008). A consequence of bilateral adrenalectomy is immediate and permanent primary adrenal insufficiency, which requires life-long glucocorticoid and mineralocorticoid replacement therapy and monitoring. Part of the management of primary adrenal insufficiency includes emergency treatment for situations of acute stress such as sepsis or trauma. These events can be life-threatening if not treated with high "stress doses" of these hormones intravenously. Additionally, Nelson's syndrome is a potential complication of bilateral adrenalectomy that is marked by progressive pituitary corticotroph growth and rising ACTH levels. This can be a serious complication because it may result in compression of structures adjacent to the pituitary gland within or above the sella turcica, and pituitary apoplexy, although this ultimate complication should not occur in the modern era when close follow-up with pituitary MRI allows early detection of corticotroph tumor growth (Assie, et al 2007).

1.1.3 Unmet medical need

There is still much room for improvement beyond the existing medical therapies, because substantial subsets of patients either do not achieve normalization of mUFC or have adverse reactions from the medical therapy.

Therefore, there is an unmet medical need to develop new drugs with improved safety and efficacy. Based on the data from study LCI699C2201 in patients with Cushing's disease, osilodrostat shows promise in fulfilling this unmet medical need.

1.2 Introduction to investigational treatment, osilodrostat

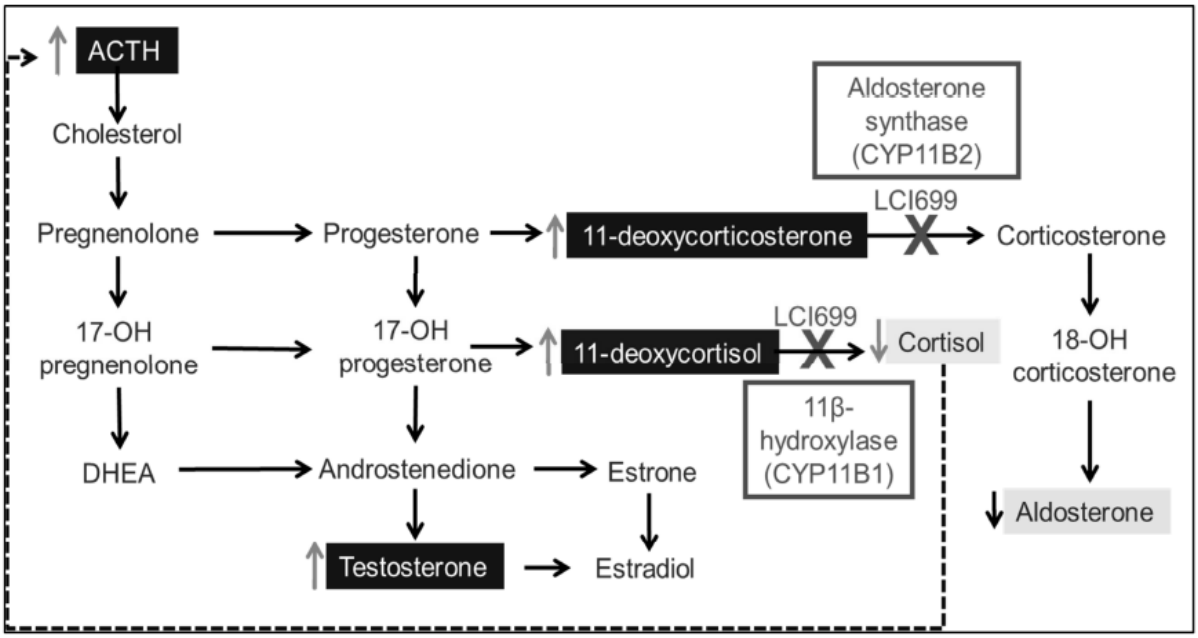
1.2.1 Overview of osilodrostat

Osilodrostat (company research code: LCI699) 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 Cushing's syndrome. The current development activity of osilodrostat is focused on the treatment of patients with Cushing's disease (hypercortisolism due to a pituitary corticotroph adenoma), because it is the most common cause of Cushing's syndrome and it is a relatively homogeneous patient group. 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 III study.

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

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



1.2.1.1 Non-clinical experience

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

1.2.1.1.1 Non-clinical Pharmacology

The oral absorption of 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 the *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 [LCI699C2102] are summarized in Section 1.2.1.2.1. It is unlikely that osilodrostat will increase the systemic exposure of co-medications whose clearance is mediated by P-gp, BCRP, OAT1, OAT3, OCT1, and OCT2 transport activity.

1.2.1.1.2 Preclinical Safety

Safety pharmacology:

In safety pharmacology studies, proarrhythmic indices and QTc interval prolongation were observed in an *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 an 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 (EFD in rats and rabbits, FEED 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 Cushing's disease patients. For detailed information, please refer to the [Investigator's Brochure].

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 [LCI699A2101]. 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) [LCI699C2101]. Results from a cocktail drug-drug interaction study [LCI699C2102] showed that at a single dose of 50 mg which covers the exposure at the highest therapeutic dose of 30 mg b.i.d. at steady state, osilodrostat is a moderate inhibitor of CYP1A2, a weak to moderate inhibitor of CYP2C19, and a weak inhibitor of CYP2D6 and CYP3A4/5.

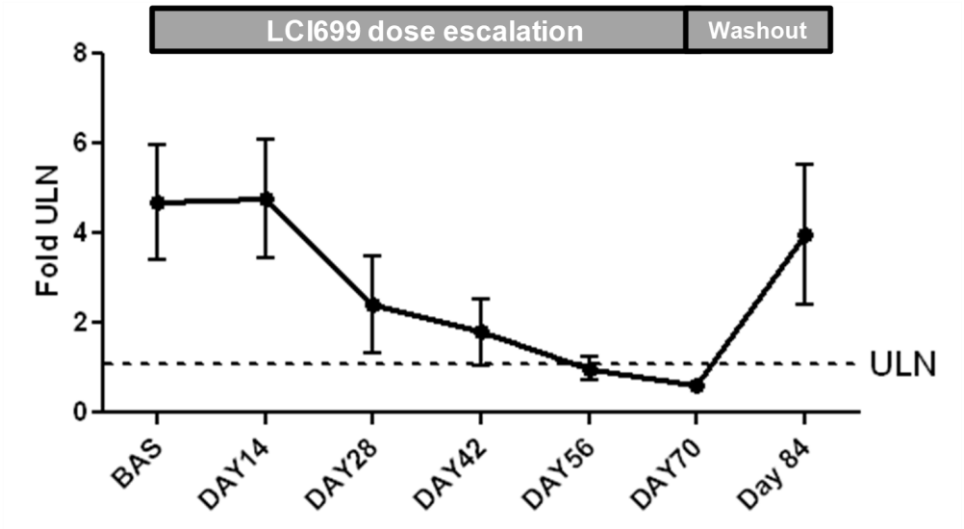
1.2.1.2.2 Results of LCI699C2201 study in Cushing's disease

The purpose of the LCI699C2201 study was to determine whether the ability of osilodrostat to inhibit 11β-hydroxlase could safely reduce urinary free cortisol (UFC) in patients with Cushing's disease. This was initially studied over a 10-week treatment duration Proof-of Concept (Part I). Part II of the study aimed to further evaluate the observations from the Part I by enrolling a cohort of patients who participated in Part I and a new cohort (Expansion cohort) of patients, and evaluating the long-term efficacy and safety of osilodrostat treatment.

In Part I, osilodrostat was effective in controlling cortisol production in all 12 patients studied. At daily osilodrostat doses between 2 mg 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).

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

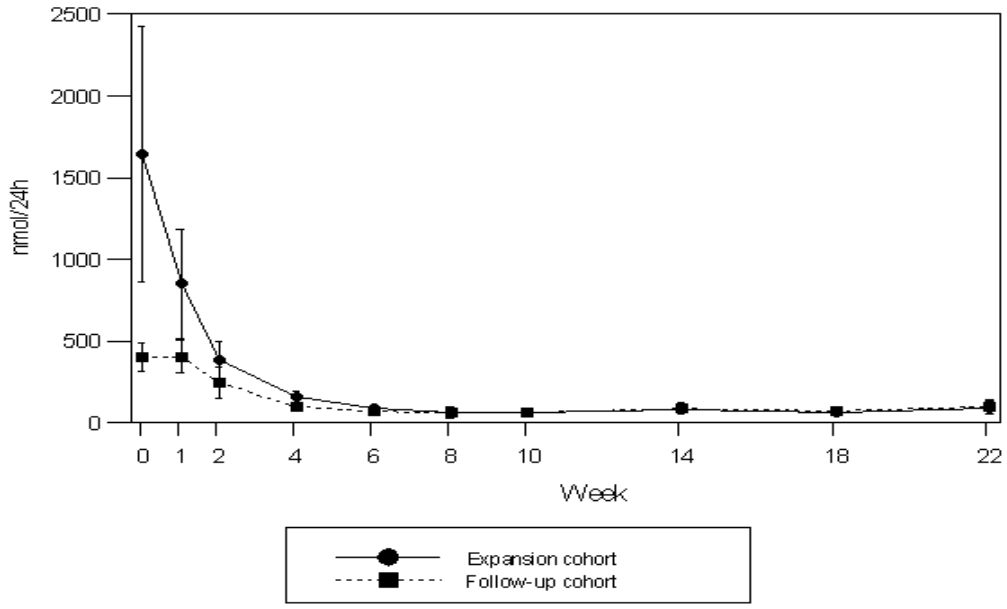


Source: In-text Figure 11-2, 10-week interim CSR study [LCI699C2201]

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

In Part II, 17 out of 19 patients completed 22 weeks of treatment and 15 had normal 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 [LCI699C2201]

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. Adverse events (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 Study [CLCI699C2201], in patients with Cushing's disease, safety data from the 10-week analysis also showed that osilodrostat was well tolerated with similar common adverse events to those in the hypertension trials, including: fatigue, nausea, vomiting, diarrhea, headache, dizziness, hypokalemia and muscle spasms.

In Part I of the study [LCI699C2201], 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 throughout the study. Of the 19 enrolled patients, 17 patients completed the 22 weeks treatment period with a median duration of exposure of 25.1 and 38.9 weeks in the Expansion cohort and Follow-up cohort, respectively. The safety findings identified in the interim analysis (data cut-off date: 23-Dec-2013) that was

performed after the last patient had completed 22 weeks of treatment in this ongoing study are summarized below.

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 increase levels of oxycorticosteroids, blood corticotrophin, and blood testosterone were the most common AEs suspected to be drug related (by PT).

Two patients experienced a total of 3 SAEs.

One patient was reported to have grade 3 pituitary-dependent Cushing's syndrome (preferred term [PT]). 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 (PT)) and grade 1 Electrocardiogram QT prolongation (PT). 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 electrocardiogram QT prolongation SAE was ongoing at the time of the data cut-off date.

One patient discontinued the study drug due to AEs. This patient reported (by PT) 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.

Nine patients reported AEs requiring dose adjustment or study drug interruption with adrenal insufficiency and fatigue being the most commonly reported. The majority of AEs requiring does adjustment or study-drug interruption was suspected to be related to study drug, were mainly grade 1 and resolved after the dose was adjusted or temporarily interrupted.

Nine patients reported AEs of special interest with adrenal insufficiency, acne, and hirsutism (female only) being the most commonly reported. The majority of AEs of special interest were suspected to be related to study drug, were mainly grade 1/2 and resolved after the dose was adjusted or temporarily interrupted, with concomitant medication or without any action being taken.

All patients in the study had at least one clinical laboratory test result outside the normal range at some point, changes were grade 1/2 in most of the cases. There were no clinically relevant changes over time observed for mean values of clinical laboratory tests. No patients discontinued the study drug due to abnormal clinical laboratory parameters. There were trends towards decreased fasting plasma glucose, HbA1c, cholesterol and triglyceride levels.

There were no clinically relevant changes in mean vital signs. There were no clinically relevant changes from baseline in mean QTcF or in the other mean ECG intervals.

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

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

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

1.2.1.2.4 Osilodrostat: QT/QTc in healthy volunteers

The cardiac repolarization liability of osilodrostat was assessed in the definitive ICH E14 compliant thorough QT Study (TQT) study CLCI699C2105 in 86 healthy male and female subjects. A maximum mean ΔΔQTcF of 25.4 ms was observed on osilodrostat 150 mg (5-fold higher than the maximum clinical dose of 30 mg), with absence of a relevant QT effect on osilodrostat 10 mg (ΔΔQTcF 0.3 ms; 90% CI −1.50, 2.16). No subject experienced QTcF values >500 ms, or increases from baseline >60 ms. The maximum effect was observed at Tmax (1 hour post-dose). No dose-related effects were observed for the cardiac intervals (QRS, PR, or HR), or on blood pressure on osilodrostat 10 mg or 150 mg. No new safety concerns were identified in this study.

A population-PK analysis was performed to estimate the peak exposure (Cmax) of the highest planned clinical doses of osilodrostat (20 mg and 30 mg), based on the pooled PK data from the osilodrostat studies A2101, C2105, and C2201 (total N=178). The predicted arithmetic mean and geometric mean Cmax,ss of osilodrostat 20 mg was 174 and 168 ng/mL, and on osilodrostat 30 mg was 284 and 275 ng/mL, respectively.

The concentration-QTcF effect model from study LCI699C2105 was then applied to the predicted Cmax values for osilodrostat 20 mg and 30 mg from the Population-PK analysis. Based on the predicted exposure levels, the predicted maximum mean QTcF on osilodrostat 20 mg is 4.1 ms (CI 2.98, 5.28), and the predicted maximum mean QTcF on osilodrostat 30 mg is 6.3 ms (CI 5.13, 7.42).

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

2 Rationale

2.1 Study rationale and purpose

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 Cushing's syndrome (CS) of which the most common cause is an ACTH-secreting pituitary adenoma (Cushing's disease [CD]).

This is a pivotal, Phase III, global, multi-center, randomized, double-blind, placebo-controlled study to confirm the results of the phase II [LCI699C2201] study and intended to support the registration of osilodrostat for the treatment of patients with CD who are candidates for medical therapy.

2.2 Rationale for the study design

2.2.1 Overall design

The study aims to demonstrate the superiority of osilodrostat compared to placebo in achieving a complete response (mUFC ≤ ULN) at Week 12, to evaluate the safety of osilodrostat compared to placebo, and to evaluate the long-term safety and efficacy of osilodrostat.

2.2.2 Period 1: Double-blind, placebo-controlled

At the beginning of the 12-week placebo-controlled period, eligible patients will be randomly assigned in a double-blinded fashion, either to osilodrostat treatment or to placebo (2:1 ratio). The duration of the placebo-controlled period in the current study is optimized to allow for appropriate dose titration and collection of placebo-controlled data, while minimizing the duration of time without cortisol-lowering therapy to protect patient safety. Furthermore, over 75% of patients in the Phase II study [LCI699C2201] had UFC controlled by Week 6 and all patients had completed up-titration by Week 8.

The placebo-controlled study design assesses efficacy and safety in patients randomized to treatment with osilodrostat versus placebo during the first 12 weeks of the study. The double-blind design minimizes the risk of potential bias. It also provides data to distinguish adverse effects related to the study drug from those resulting from underlying disease.

In order to maintain the integrity of the blind during the first 12 weeks of the study:

1. UFC and related laboratory tests obtained during Period 1 that may disclose treatment assignment will remain blinded (as described in Section 6.5.3) to patients, investigators and Novartis Clinical Trial Team until after the 48-week Core database lock.
2. Matching placebos will be provided for all tablet strengths used during Period 1 (osilodrostat 1 mg, 5 mg, 10 mg, and (depending on availability) 20 mg).
3. Patients randomized to placebo will undergo mock titration (simulating both up and down-titrations) consistent with what may occur in patients treated with active drug during Period 1. Please see Section 6.2.1 for details.

In addition, to reduce the risk of premature discontinuation during the placebo-controlled period, comorbidities (such as hypertension, hyperglycemia, hyperlipidemia and hypokalemia), should be optimally treated prior to study entry and during the entire study. Rescue therapy for co-morbid conditions should also be implemented before a decision is made to discontinue a patient from study drug (see rescue plan in Section 6.1.3). During this period, the investigator may temporarily interrupt study drug in the event of an AE of suspected adrenal insufficiency, or any AE that requires replacement or stress doses of glucocorticoid therapy (for additional information, see Section 6.2, Section 6.3.1 and Section 6.3.2).

2.2.3 Period 2: Open-label

The objective of the open-label period, during which all patients receive active drug, is to elucidate the long-term efficacy and safety profile of osilodrostat while allowing for dose titration as needed by the investigator to achieve optimal control.

To maintain the integrity of the blind during Period 1 (double-blind period), at the beginning of Period 2 (Week 12, open-label period) all patients will start open-label osilodrostat 2 mg b.i.d., except those treated with doses < 2 mg b.i.d. at the end of Period 1. The first UFC results available to investigators will be for the Week 14 assessment, which occurs 2 weeks after these patients have received osilodrostat 2 mg b.i.d. Based on experience from the Phase II study, the majority of patients treated with active drug during Period 1 are expected to have been titrated to doses of > 2 mg b.i.d. by week 12. Decreasing the dose to 2 mg b.i.d. in these patients at the beginning of Period 2 is likely to lead to increased mUFC values in the Week 14 urine sample. On the other hand, patients randomized to placebo would have been on active treatment for 2 weeks and their mUFC values will likely have fallen from baseline. Thus, it is expected that mUFC values at Week 14 will overlap significantly between the two treatment groups, thereby maintaining the integrity of the blind.

During Period 1, a small subset of osilodrostat- and placebo-treated patients may have been down-titrated to doses lower than 2 mg b.i.d. by week 12. At the start of Period 2 (after Week 12 assessments have been completed), these patients will continue or start treatment with open-label osilodrostat at their last dose of Period 1 with dose titrations based on mUFC at Week 14 onwards (as described in Section 6.2).

2.2.4 Optional Extension Phase

At the end of the Core study (Week 48) patients receiving clinical benefit from osilodrostat have the option to enter a 48-week optional Extension phase (Weeks 48 to 96). Additional safety and efficacy data will be collected during this period. Patients currently enrolled in the optional extension phase must end study participation within 4 weeks after Protocol Amendment 02 is approved at the site, or by Week 96, whichever occurs first. Refer to Section 4.1 for more details.

2.2.5 Steps to ensure reliability of UFC results

As UFC, measured in a 24-hour urine collection is the biomarker used for both the primary and key secondary assessments, special care is taken to ensure that the results are reliable (Section 7.2.1.1). The 24-hour urine collection must be within defined upper and lower limits for urine volume (>500mL - <3000mL) and urine creatinine (see Laboratory Manual for the most current reference ranges). These limits are intended to avoid the reporting of misleading results because of incomplete urine collections or extremes of urine concentration from under-treatment or overtreatment of central diabetes insipidus if present. In addition, patients with eGFR < 60 mL/min are excluded because reduced urine free cortisol excretion has been reported in patients with moderate or severe renal impairment (Chan, et al 2004; Issa, et al 1999; and Sharp, et al 1996). Additionally, the method used for measurement of UFC at the central laboratory is liquid chromatography-tandem mass spectrometry (LC-MS/MS). In contrast to immunoassays, LC-MS/MS has the advantage of measuring cortisol accurately and exclusively, without concern of

interference by cross-reactivity of accumulating cortisol precursors (e.g., 11-DOC) with osilodrostat therapy (Trainer, et al 2014; Monaghan, et al 2011).

2.2.6 ECG Monitoring

Cardiac monitoring will include 12-lead Safety ECGs at pre-dose (Day 1) and 1.5 hours post-dose at each visit the patient receives study drug. The Safety ECGs are the primary cardiac safety assessment, and their rationale is to assess the maximum change in QTcF in each individual patient each time they receive study drug at the site. The 12-lead safety ECGs are read in real-time on-site by the PI or other qualified physician (e.g., cardiologist), and if there is QT prolongation (QTcF > 480 ms or increase > 60 ms from baseline assessment), patients are to be managed according to the QT Monitoring Flow Chart in Figure 7-2.

In addition, 24-hour continuous 12-lead Holter recordings will be performed at baseline, Weeks 2, 12, 14, 36, and as applicable at Week 72 and at the end of treatment visit in the optional Extension phase. The 24 hour Holter assessments are not intended to provide real-time assessment of cardiac intervals and cardiac rhythm; the recordings are read centrally.

2.3 Rationale for dose and regimen selection

The rationale for b.i.d. dosing of osilodrostat is based on its half-life of 3-5h. This dosing regimen was used in study [LCI699C2201]. The original modeling of PK exposure estimated that a dose of 4-5 mg b.i.d. was expected to achieve a plasma concentration above the *in vitro* IC50 for CYP11B1 (2.5 nM) for a full 24 hours for efficacy; however, 2 mg b.i.d was chosen to be the starting dose in the proof-of-concept study based on safety considerations.

In the Phase II study [LCI699C2201], Part I, evaluating osilodrostat in patients with uncontrolled CD over a 10 week period (N=12), osilodrostat was initiated at 2 mg b.i.d with dose escalation every 2 weeks to 5, 10, 20, and 50 mg b.i.d until UFC was normalized. All patients normalized UFC at least once during the study and 11/12 patients had a normal UFC at week 10. The mean dose at the time of response was 13.5 mg/day (SD = 13.9 mg), and the mean time to response was 34.3 days (SD = 14.1 days). The daily dose required to first reach UFC normalization was ≤ 20 mg/day in 75% of the patients, with at least 50% of the patients requiring 10-20 mg/day (5-10 mg, b.i.d).

In Part II (N=19), osilodrostat was initiated at 2 or 5 mg b.i.d. in 15 new patients with dose escalation every 2 weeks to 5, 10, 20 and 30 mg b.i.d until UFC normalization, and at the penultimate effective dose in 4 patients from Part 1 with escalation if needed. All patients normalized UFC at least once during the study; 16/19 (84%) patients had a normal UFC at Week 10, and 15/19 (79%) had a normal UFC at Week 22. The distribution of total daily doses was similar to that of study Part I. The mean total daily dose for the 17 patients that remained in the study at Week 22 was 16.9 mg; the total daily dose at Week 22 was ≤ 20mg in 14/17 (82.3%) of patients.

Hypocortisolism was reported in 4 patients in Part I of study [LCI699C2201], and in 6 patients in Part II (Core). Hypocortisolism resolved in all patients with dose reduction and/or interruption. In addition, during Part II of study [LCI699C2201], one patient had biochemical evidence of hypocortisolism on 2 mg b.i.d., and the dose was reduced to 1 mg b.i.d. Therefore, the individual dose titration starting at 2 mg b.i.d. is an appropriate method to assess the efficacy

and safety of osilodrostat. In the event that hypocortisolism (24-hour mUFC < LLN, or mUFC in the lower part of the normal range with signs and symptoms of adrenal insufficiency) is observed on a dose of 2 mg b.i.d., the dose may be reduced to < 2 mg b.i.d. (i.e., 1 mg b.i.d., 1 mg q.d., or 1 mg q.o.d. (every other day)) to mitigate the risk of persistent hypocortisolism.

In both parts of this study, the interpatient variability in dose requirements to normalize cortisol is broad (e.g. 2 mg b.i.d. to 30 mg b.i.d.). Fixed-dose comparisons of treatment groups with various doses of osilodrostat are not appropriate because this would carry the potential risk of acute adrenal insufficiency if a relatively high dose is administered to a patient that is sensitive to osilodrostat.

This study will start individual dose titration with 2 mg b.i.d., and up-titration to 5 mg b.i.d., 10 mg b.i.d., and 20 mg b.i.d. primarily on the basis of the mUFC levels. Similar dose titration will be performed in Period 2 with dose escalation up to 30 mg b.i.d.

2.4 Rationale for choice of combination drugs

Not applicable.

2.5 Rationale for choice of comparators drugs

The placebo-controlled study design assesses efficacy and safety in patients randomized to treatment with osilodrostat versus placebo during the first 12 weeks of the study. The double-blind design minimizes the risk of potential bias.

2.6 Benefit-Risk Assessment of osilodrostat in study population

Potential patient benefits

There is an unmet medical need in patients with Cushing's disease which is a rare and serious disease with limited options for medical therapy. Phase 2 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 patients with uncontrolled Cushing's disease.

Study-specific risks

Study-specific risks in study LCI699C2302 include the potential for prolonged periods of uncontrolled hypercortisolism during washout, blinded placebo and dose titration with a maximum combined duration of under-treatment of 7 months.

To mitigate the risk of uncontrolled hypercortisolism during drug washout, patients are to be monitored closely with specific attention to controlling co-morbidities. In addition, specific exclusion criteria with regard to blood pressure and diabetes control are used. 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 (see Section 5.2).

To reduce the probability of treatment with placebo, a 2:1 randomization ratio (osilodrostat: placebo) has been implemented. In addition, close clinical monitoring of co-morbidities during

the placebo-controlled period, specific rescue therapies to treat uncontrolled co-morbidities, and criteria for early discontinuation have been implemented. In addition, the threshold for mUFC to enter the study is > 1.3 x ULN (compared to > 1.5 x ULN in other studies) allowing patients with less severe Cushing's disease to participate in the study. Furthermore, the placebo-controlled period has been kept to a minimum at 12-weeks after which patients randomized to placebo will be treated with active drug.

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.

Potential risks of osilodrostat treatment in study population

Potential risks of treatment with osilodrostat in patients with Cushing's disease 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. Corticotroph tumor progression, with or without compressive symptoms, is another potential risk. Skin rash has also been observed.

Mitigation of the potential 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 salivary cortisol levels, 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, pituitary MRI scans, and bone mineral density.

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. PK sampling will be conducted in all patients to measure osilodrostat plasma concentrations and assess for any correlation with adverse events or for potential drug-drug interaction.

Oversight Committees

A Steering Committee has been established comprising investigators who are Cushing's disease experts, whose role is to contribute to the study design, oversee the conduct of the study and to ensure the transparent management of the study according to the protocol. An independent data monitoring committee (DMC) comprising external endocrinologists with expertise in Cushing's disease, a cardiologist and a statistician will be established before FPFV to monitor

unblinded safety data periodically as the study proceeds, and to oversee the functioning of the IEs. A Novartis Safety Management Team (SMT) exists to review and evaluate all emerging safety data for potential new safety signals on a regular basis and to evaluate safety management across the program.

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, including those randomized to the placebo arm.

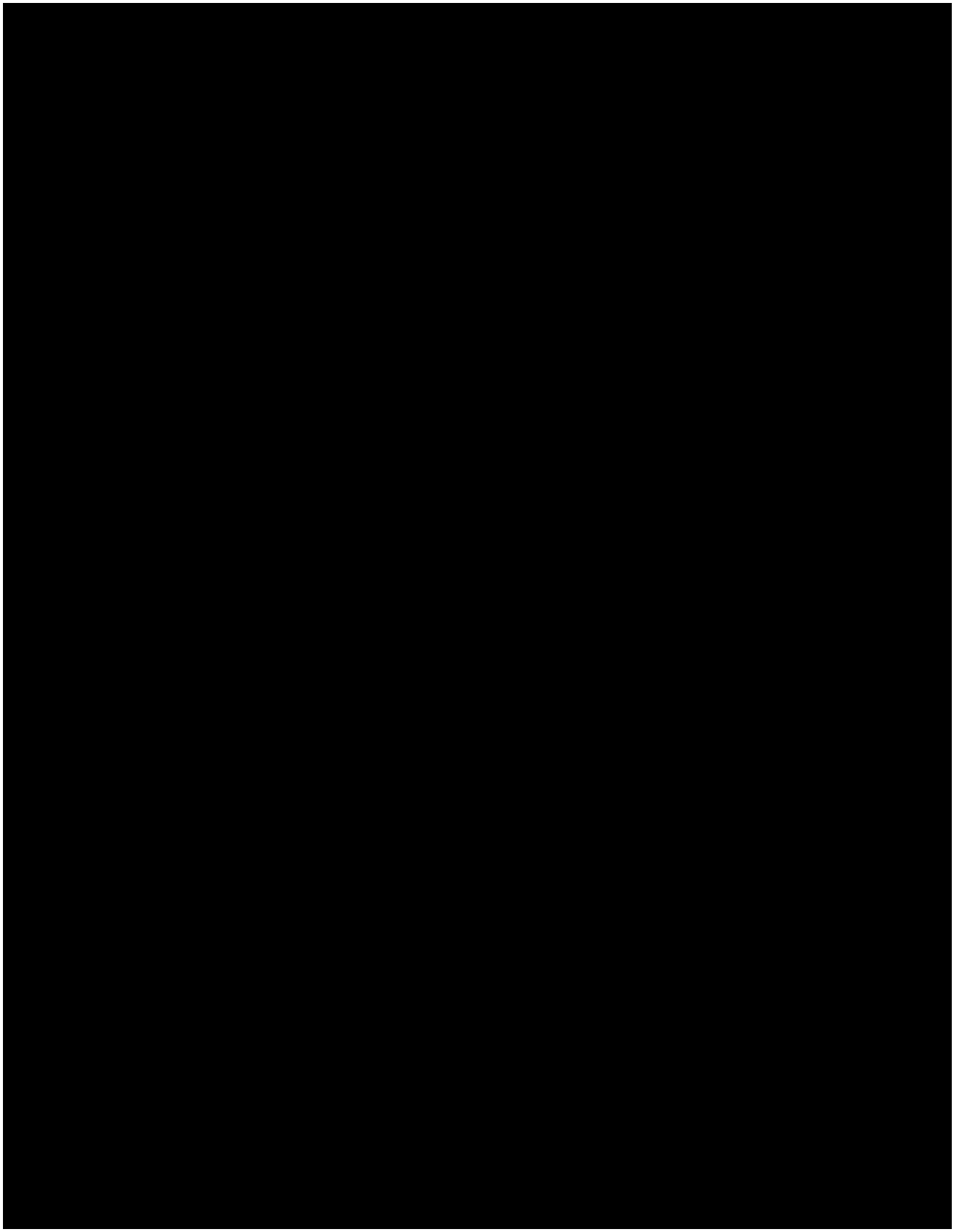
2.7 Biomarker development

24-hour UFC is currently the standard test for screening and monitoring Cushing's disease. Since cortisol is not uniformly secreted during the day, a quantitatively exact collection and measurement of 24-hour urine is required to detect abnormal cortisol levels.

Although this method has been used in routine clinical practice for many years, there are several practical/methodological difficulties accompanying the collection and analyses of 24-hour UFC samples. For instance, patient education and compliance is essential to ensure that 24-hour urine samples are collected correctly, and consequently the UFC results are reliable. UFC levels could be elevated by physiological or pathological conditions other than Cushing's disease (pseudo-Cushing's syndrome, e.g., due to major depression or chronic alcoholism). Multiple UFC collections are required to assess the possibility of cyclic hypercortisolism. Salivary cortisol may allow an easier method of assessing cortisol that reflects the concurrent free cortisol level in serum. Hair cortisol levels may be useful to assess longer-term overall cortisol secretion.

This study will assess the value of additional pharmacodynamic markers such as the [redacted] salivary cortisol, and hair cortisol.

[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		Refer to Section 10.4
To demonstrate the superiority of osilodrostat compared to placebo in achieving a complete response (mUFC ≤ ULN) at Week 12.	The proportion of randomized patients with a complete response, i.e. mUFC ≤ ULN at Week 12.	
Key secondary		Refer to Section 10.5.1
To assess the complete response rate in both arms combined at Week 36 in patients receiving osilodrostat treatment.	The proportion of patients with mUFC ≤ ULN at Week 36 for combined randomized patients who receive osilodrostat treatment.	
Other secondary		Refer to Section 10.5.2
To assess the proportion of patients with a complete response (mUFC ≤ ULN) or a partial response (mUFC decrease ≥ 50% from baseline and > ULN) at Week 12, Week 36, and Week 48.	The overall response rate defined as proportion of complete responders (mUFC ≤ ULN) plus partial responders (≥ 50% reduction in mUFC from baseline and > ULN) at Week 12, Week 36, and Week 48 by treatment arms and for all patients.	
To assess the change in mUFC during the Core and Extension periods of the study. (Refer to Table 7-1a and Table 7-2 for the study visit and evaluation schedule during the Core and optional Extension phases, respectively).	Actual and percentage change in mUFC from baseline to each post-baseline visit during the Core and Extension at which UFC is collected by treatment arms and for all patients.	
To compare the time-to-first control of mUFC during the placebo-controlled period (Weeks 1-12) between the randomized treatment arms.	Time-to-first control of mUFC, which is defined as the time (in days) from randomization to the first mUFC collection that was ≤ ULN before completion or discontinuation of placebo-controlled period, whichever is earlier.	
To assess the time-to-escape during osilodrostat treatment up to Week 48.	Time-to-escape is defined as the time (in weeks) from the first collection of normal mUFC (≤ ULN) to the first mUFC > 1.3 x ULN on two consecutive visits on the highest tolerated dose of osilodrostat and not related to a dose interruption or dose reduction due to safety reasons. Escape will not be assessed for patients during the first 26 weeks.	

Objective	Endpoint	Analysis
To assess cardiovascular and metabolic related parameters associated with CD (fasting plasma glucose, HbA1c, fasting lipid profile, blood pressure, weight and waist circumference) by assessing actual and percent change from baseline and shift table at Weeks 12, 36, and 48.	The actual and percent change from baseline in fasting plasma glucose (FPG), HbA1c, fasting lipid profile, blood pressure (BP), weight and waist circumference at Week12, Week 36, and Week 48 by treatment arms and for the overall patient population.	
To assess the change from baseline at Weeks 12, 36, and 48 in physical features of CD.	Mean change from baseline to Week 12, Week 36, and Week 48 in each of the following clinical signs of Cushing's disease, captured by: a semi-quantitative Likert scale for facial rubor, striae, supraclavicular fat pad, dorsal fat pad, proximal muscle wasting (atrophy), central (abdominal) obesity, and ecchymoses (bruises) by randomized treatment arm and overall population.	
To assess the change from baseline in bone mineral density (BMD) by DXA scan at the lumbar spine and total hip at Week 48.	The change from baseline in bone mineral density, and BMD T-score, at the lumbar spine (L1-L4) and total hip at Week 48 by treatment arm and for overall patient population.	
To determine the safety and tolerability of osilodrostat in the study population.	Adverse events and laboratory abnormalities. Assessed events include: AEs of special interest, laboratory evaluation, ECG, Holter recording, and pituitary MRI.	
To assess the change from baseline in Health Related Quality of Life, as measured by the CD-specific QoL questionnaire (CushingQoL); by the Beck Depression Inventory (BDI-II); and by the general health-related QoL instrument EQ-5D-5L, by randomized treatment arm and overall.	Change in standardized score of CushingQoL, Beck Depression Inventory-II, and EQ-5D-5L, from baseline to Week 12 and Week 48, from Week 12 to Week 36, and from Week 36 to Week 48, or the last measurement prior to early discontinuation, whichever occurs earlier.	
To evaluate pharmacokinetic exposure of osilodrostat in the study population.	Plasma concentrations (pre-dose, 1-2 h post-dose) of osilodrostat.	
To assess the change from baseline in serum, salivary and hair cortisol levels	The actual and percentage change from baseline in serum cortisol, late night salivary cortisol, morning salivary cortisol and hair cortisol levels for every visit in the Core and extension phases at which the biomarkers of hypercortisolism are collected, by treatment arms and for all patients.	

Objective	Endpoint	Analysis
[redacted]		

4 Study design

4.1 Description of study design

This is a Phase III, global, multi-center, randomized, double-blind, placebo-controlled study. The study design is placebo-controlled during the first 12 weeks, followed by open-label treatment with osilodrostat until week 48, and an optional Extension phase.

Screening period (up to 8 weeks):

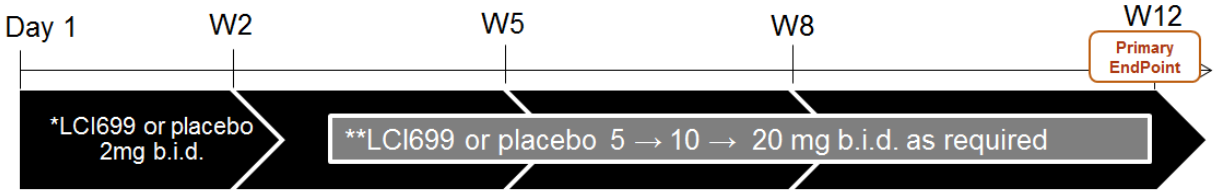
The screening period will have a maximum duration of 8 weeks to enable patients to washout their current treatment for Cushing's disease. Patients will be evaluated for trial eligibility after the washout period is completed.

During washout, some patients may have loss of control of co-morbidities such as hypertension and diabetes. Therefore the screening period should be viewed as a "run-in" period in which the treatment of co-morbidities is optimized. Patients should be closely monitored and treated accordingly, aiming ideally for normalization of blood pressure, fasting glucose and potassium. Control of co-morbidities in this "run-in" is important for patient safety and to ensure the majority of patients can complete the 12-week placebo-control period and therefore minimize loss of data. Three 24-hr UFC urine samples and two late night salivary cortisol samples are to be collected after completion of the washout period to assess study eligibility.

Period 1 (Weeks 1-12): double-blind, placebo-controlled period

This is the randomized, double-blind, placebo-controlled period (Weeks 1-12). Eligible patients are randomized in a 2:1 ratio to treatment with study drug (osilodrostat or placebo, respectively). Patients are stratified at randomization according to history of pituitary irradiation (yes/no).

Figure 4-1 Schematic of Period 1

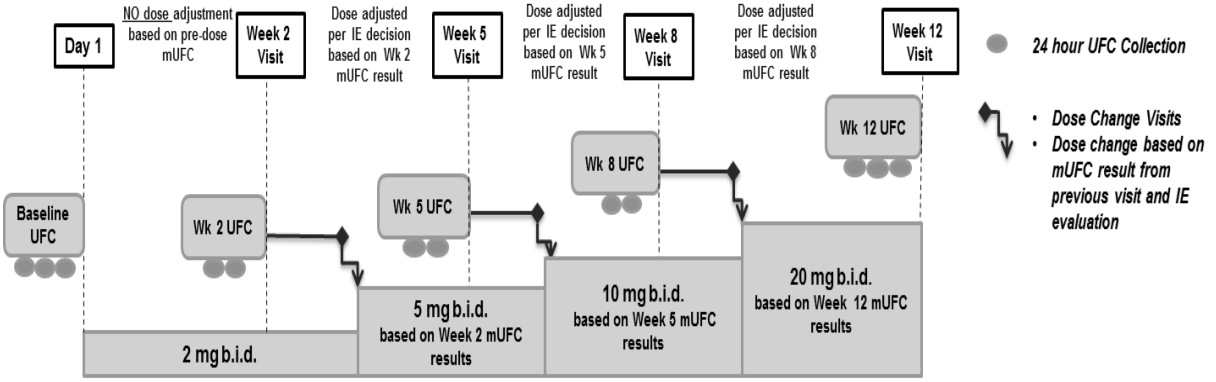


*Patients are randomized in a 2:1 ratio to osilodrostat (LCI699) or placebo
** LCI699 Dose determined by Independent Endocrinologists. Intermediate doses may be used in specific circumstances. Please see Section 6.2 for details.

Study visits occur at Day 1, and Weeks 2, 5, 8, and 12 (Figure 4-1). Study drug is started on Day 1 at a dose of 2 mg b.i.d., and titrated according to the regimen described in Section 6.2, to a dose which lowers mUFC to within the normal range. Dose adjustments, if required, will be determined between study visits allowing the UFC samples collected just prior to the next visit to reflect the dose adjustment. The maximum dose that can be reached in Period 1 is 20 mg b.i.d. After Week 2, visit intervals are increased to three or more weeks to ensure adequate time

to execute the required steps for dose adjustment, which include provision of the laboratory data and clinical information to the IE, time for the IE to determine study drug dose and communicate this to sites, and for sites to contact the patient to implement the dose to patients.

Figure 4-2 Timing of study visits, UFC collection, and dose adjustments during Period 1



Legend: During Period 1, study visits are at Day 1 and Weeks 2, 5, 8, and 12. The IE determines the study dose once UFC results become available. Patients may be informed of dose changes by a site phone contact or at a visit if the patient needs to receive new study drug supplies or for safety issues. See text for additional details.

Three 24-hour urine samples will be collected by patients, preferably on consecutive days at screening, immediately prior to Day 1 and the Week 12 visit (primary endpoint) during this study period. Two 24-hour urine samples will be collected preferably on consecutive days immediately prior to each of the other visits (i.e. at Weeks 2, 5, and 8).

In order to maintain the treatment blind during Period 1, all laboratory results obtained during Period 1 that may disclose the randomized treatment assignment are blinded to patients, investigators and the Novartis Clinical Trial Team (see Section 6.5.3 for further details). The relevant laboratory results that are blinded include: UFC, urine creatinine, serum and salivary cortisol, ACTH, aldosterone, renin, estradiol, estrone, androgens (testosterone, delta-4 androstenedione, DHEAS), and precursors 11-deoxycortisol, 11- deoxycorticosterone.

A group of independent endocrinologists (IEs) is responsible for managing dose titrations during Period 1 between visits. Titrations for patients assigned to placebo will aim to simulate the active arm. Refer to Section 6.2 for details on dose titration. The IE communicates study drug dosing instructions to the site for all patients (active and placebo) in a blinded manner through the IRT system. If a dose adjustment is required, sites may inform patients of a dose change by phone or at a visit if the change can be managed with the patients' current supplies. If a different tablet strength is needed to implement the dose change, patients need to return to the site to collect the required study drug supplies and instructions on how to administer the dose. To minimize dosing errors for patient safety, it is **very important** that these instructions are clear, simple and written legibly (see Section 6.2.1.4. and Section 6.6 for further details).

If patients discontinue study drug treatment before the Week 12 visit, investigators should make reasonable efforts to follow patients and perform assessments for all scheduled visits up to and

including the Week 12 visit (as listed in Table 7-1a, Post-treatment Follow-up), even if alternative cortisol lowering therapy has been initiated.

During Period 1, the investigator may temporarily interrupt study drug in the event of an AE of suspected adrenal insufficiency, or any AE that requires replacement or stress doses of glucocorticoid therapy (for additional information, see Section 6.2.1.2 and Section 6.3.1).

Period 2 (Weeks 12-48): single arm, open-label treatment period

Period 2 starts immediately after the Week 12 visit, when the trial becomes open-label with all patients receiving the active drug, osilodrostat. During Period 2 patients randomized to placebo switch to osilodrostat and undergo their first dose titration with active drug, while patients randomized to osilodrostat continue this treatment and undergo a "second" dose titration.

- All patients on doses of ≥2 mg b.i.d. at the Week 12 visit will receive open-label osilodrostat at a starting dose of 2 mg b.i.d. at the beginning of Period 2, regardless of treatment assignment in Period 1.
- Patients on <2 mg b.i.d. at the Week 12 visit will continue the same dose they were on at the end of Period 1, regardless of treatment assignment during Period 1.
- Placebo-treated patients on a dose of < 2 mg b.i.d. at the end of Period 1, will continue this dose but with active drug at the beginning of Period 2.

During Period 2, the investigator is responsible for dose titration, which will be based on mUFC and other relevant patient data (as described in Section 6.2.2). Osilodrostat can be titrated up to a maximum dose of 30 mg b.i.d. during this period. The investigator has access to all laboratory results from the Week 14 assessments onward. The IE does not participate in dose decisions beyond Week 12.

Three 24-hour urine samples will be collected by patients, preferably on consecutive days immediately prior to the Week 36 visit (key secondary endpoint) and Week 48 (end of Core phase). Two 24-hour samples will be collected prior to all other visits in Period 2. A patient is considered to have reached a stable efficacious dose when mUFC remains ≤ ULN. This dose is continued, unless a change is needed (see Section 6.2.2 for details). As in Period 1 dose adjustments may be managed via a phone call, however if a different tablet strength is needed patients should return to the site to collect the new supplies.

Optional Extension phase:

At Week 48, patients have the option to enter an optional open-label Extension phase. Patients who do not enter the optional extension discontinue osilodrostat at Week 48 and conclude with a Post-Treatment (End of Study) visit after 30 days off study drug. Patients enrolled in the optional extension phase must end study participation within 4 weeks after Protocol Amendment 02 is approved at the site, or by Week 96, whichever occurs first. ~~If~~ Patients who are benefitting from study treatment, have the option to enter a separate long-term safety follow-up study or stop study treatment. Patients who do not enter the long-term safety follow-up study will discontinue osilodrostat and conclude the study with a Post-Treatment (End of Study) visit after 30 days off study drug. Refer to Section 6.1.5 for more details. During the optional extension phase the dose of osilodrostat will be maintained at the established effective dose

unless a change is required based on mUFC results collected at Weeks 48, and if applicable, at Weeks 60, 72, and 84 (see Section 6.2.3 for details on dose adjustment).

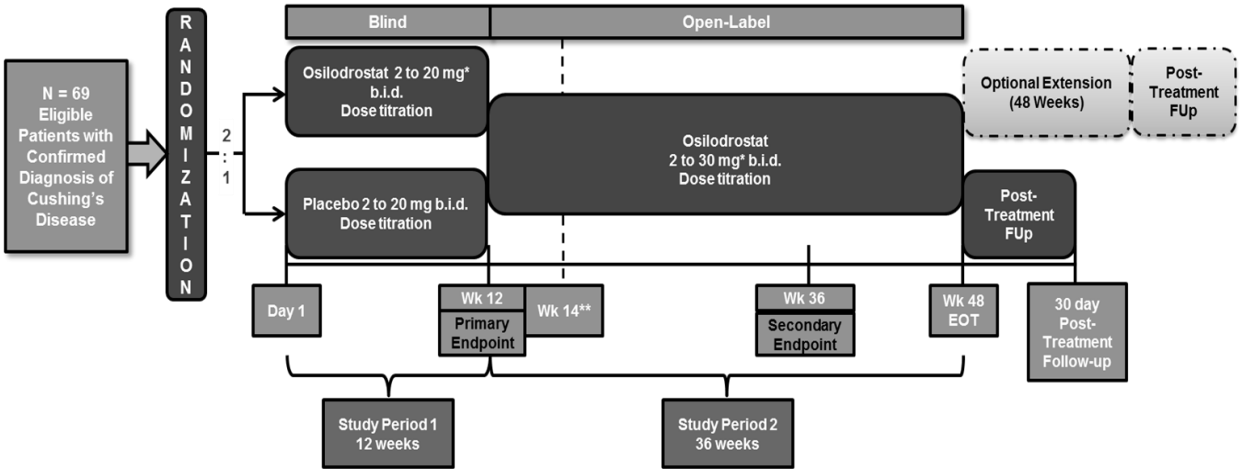
Additionally, patients are allowed to have unscheduled visits at any time in the study if needed, e.g. if they report signs and/or symptoms of hypercortisolism, adrenal insufficiency, other AEs, or need additional study drug supplies.

For more details on dosing titration, Independent Endocrinologists (IE) and Investigator interventions, please refer to Section 6.2.

A schematic diagram of the Core study design is shown below in Figure 4-3.

Every effort will be made to continue provision of osilodrostat treatment beyond this study as described in Section 4.3.

Figure 4-3 Schematic of Core study design



*If needed, the dose may also be titrated to below the 2 mg b.i.d. starting dose (e.g. 1 mg b.i.d., 1 mg q.d. or 1mg q.o.d.)
**The first UFC and lab results available to the investigator will be from samples collected prior to the week 14 visit
Fup: Follow up

4.2 Timing of interim analyses and design adaptations

The study will have no interim analysis for efficacy. The DMC will conduct periodic safety data reviews as outlined in Section 8.6.

4.3 Definition of end of the study

Completion of the study as a whole (last patient last visit) will occur once all patients have completed all assessments as per Table 7-1a, Table 7-1b (Core) and, as applicable, Table 7-2 (optional Extension), or have discontinued from the study, including Post-treatment follow-up or transition into the long-term safety follow-up study, whichever occurs first.

Patients to end participation in the optional Extension period within 4 weeks after Protocol Amendment 02 is approved at the site, or by Week 96, whichever occurs first. Refer to Section 6.1.5 for details.

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient will be contacted by the investigator or his/her designee. The patient should be seen as soon as possible and the 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.

5 Population

5.1 Patient population

The study population will be comprised of approximately 69 adult male and female patients with Cushing's disease who have persistent or recurrent hypercortisolism after primary pituitary surgery and/or irradiation, and patients with *de novo* Cushing's disease who are not surgical candidates for medical reasons, or refuse to undergo surgery or do not have access to a specialized center with experience in pituitary surgery.

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

5.2 Inclusion criteria

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

1. Written informed consent obtained before any assessment is performed.
2. Male or female patients aged 18 - 75 years.
3. Confirmed CD that is persistent or recurrent as evidenced by all of the following criteria being met (i.e., a, b, and c):
   a. mUFC > 1.3 x ULN (Mean of three 24-hour urine samples collected preferably on 3 consecutive days during screening after washout of prior medical therapy for CD (if applicable), confirmed by the central laboratory and available before Day 1), with ≥ 2 of the individual UFC values being > 1.3 x ULN.
   b. Morning plasma ACTH above Lower Limit of Normal
   c. Confirmation (based on medical history) of pituitary source of excess ACTH as defined by any one or more of the following three criteria:
      i. Histopathologic confirmation of an ACTH-staining adenoma in patients who have had prior pituitary surgery.
         OR
      ii. MRI confirmation of pituitary adenoma > 6 mm
         OR
      iii. Bilateral inferior petrosal sinus sampling (BIPSS) with either CRH or DDAVP stimulation for patients with a tumor ≤ 6mm. The criteria for a confirmatory BIPSS test are any of the following:
         - Pre-dose central to peripheral ACTH gradient > 2;

- Post-dose central to peripheral ACTH gradient > 3 after either CRH or DDAVP stimulation

4. Patients that received glucocorticoid replacement therapy must have discontinued such therapy for at least seven days or 5 half-lives prior to screening, whichever is longer.
5. Patients with *de novo* CD can be included only if they are not considered candidates for surgery (e.g., poor surgical candidates due to co-morbidities, inoperable tumors, patients who refuse to have surgical treatment, or surgical treatment is not available)
6. For patients with a history of pituitary irradiation: at least 2 years for stereotactic radiosurgery (SRS), and 3 years for conventional (fractionated) radiation, respectively, must have elapsed from the time of the most recent radiation treatment to the time of enrollment into this study.
7. Able to communicate well with the investigator, to understand and comply with the requirements of the study.
8. Washout of any current drug therapy for CD. The following minimum washout periods must be completed before baseline efficacy assessments are performed:
   a. Steroidogenesis inhibitors (ketoconazole, metyrapone): 1 week
   b. Pasireotide s.c. (immediate release formulation): 1 week
   c. Mifepristone: 3 weeks
   d. Dopamine agonists (e.g., cabergoline), or PPAR-gamma agonists (e.g., rosiglitazone, pioglitazone): 4 weeks
   e. Pasireotide LAR: 8 weeks. Rescreening can be used as needed to ensure washout is complete.
   f. Mitotane: 6 months. Rescreening can be used as needed to ensure washout is complete.

5.3 Exclusion criteria

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

1. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives at the time of enrollment, whichever is longer; or longer if required by local regulations, and for any other limitation of participation in an investigational trial based on local regulations.
2. Patients with pseudo-Cushing's syndrome. This may be diagnosed by two normal late night salivary cortisol value collected during the screening period and after washout of prior CD medication.
3. History of hypersensitivity to drugs of the same or similar chemical classes as osilodrostat.
4. History of malignancy of any organ system (other than 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 with risk factors for QTc prolongation or Torsade 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
   - concomitant medications known to prolong the QT interval

- patients with hypokalemia, hypocalcaemia, or hypomagnesaemia, if not corrected before pre-dose Day 1.

6. 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.
7. Pregnant or nursing (lactating) women.
8. 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 after completion of dosing. Highly effective contraception methods include:
   A. 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.
   B. Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study drug. In case of bilateral oophorectomy, documentation is required (e.g. operative report, pelvic ultrasound or other reliable imaging method).
   C. 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.
   D. 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 the case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study drug.

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

9. Patients likely to require adrenalectomy, pituitary surgery, or radiation therapy during the placebo-controlled period (Weeks 1-12) for the treatment of severe hypercortisolemia or pituitary tumor growth causing compression of the optic chiasm.
10. Patients with compression of the optic chiasm due to a macroadenoma or patients at high risk of compression of the optic chiasm (tumor within 2 mm of optic chiasm).
11. Patients who have a known inherited syndrome as the cause for hormone over secretion (i.e. Carney Complex, McCune-Albright syndrome, MEN-1, AIP).

12. Patients with Cushing's syndrome due to ectopic ACTH secretion or ACTH-independent (adrenal) Cushing's syndrome.
13. Patients who have undergone any major surgery within 1 month, or undergone transsphenoidal pituitary surgery within 3 months, prior to screening.
14. Hypertensive patients with uncontrolled blood pressure defined as SBP > 180 and/or DBP > 105 or not optimally treated for hypertension as judged by the investigator.
15. Diabetic patients with poorly controlled diabetes as evidenced by HbA1c > 9 % or not optimally treated for diabetes mellitus as judged by the investigator.
16. Patients who are not euthyroid as judged by the investigator.
17. Patients with moderate to severe renal impairment (estimated GFR < 60 mL/min by the MDRD formula).
18. Patients with liver disease such as cirrhosis, chronic active hepatitis, or chronic persistent hepatitis, or patients with serum ALT and/or AST > 3 x ULN, or total bilirubin > 1.5 x ULN.
19. Any ongoing or prior medical condition, drug or alcohol abuse, non-compliance behavior, or inability to complete the entire trial that can negatively interfere with the conduct of the study or the evaluation of its results as judged by the investigator.
20. Previous exposure to osilodrostat for the treatment of CD.
21. History of stroke, or pulmonary embolism within the prior year.
22. Repeated history of deep venous thrombosis unrelated to prolonged bed rest, recent surgery, or pregnancy.
23. History of psychiatric hospitalization within the prior 6 months.
24. Score "yes" on item 4 or item 5 of the Suicidal Ideation section of the Colombia Suicide Severity rating Scale (C-SSRS), if this ideation occurred in the past 6 months, or "yes" on any item of the Suicidal Behavior section, except for the "Non-Suicidal Self-Injurious Behavior" (item also included in the Suicidal Behavior section), if this behavior occurred in the past 2 years.

6 Treatment

6.1 Study drug

The study drug consists of osilodrostat (LCI699) and matching placebo, in the form of film-coated tablets for oral administration, in the following tablet strengths: 1 mg, 5 mg, 10 mg, and (depending on availability) 20 mg.

Each strength has a unique size, imprint 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 (and matching placebo) 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

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

On study visit days, patients should be reminded not to take the study drug prior to the site visit to ensure compliance with the ECG and pre-dose PK sampling procedure. The morning dose of study drug on the visit days should be administered at the site after the ECG and pre-dose PK sampling has been completed.

6.1.2 Ancillary treatments

Not applicable.

6.1.3 Rescue medication for co-morbid conditions

Patients should receive optimal treatment for co-morbidities (hyperglycemia, hypertension, dyslipidemia, hypokalemia) both during the screening period and study treatment period. During the placebo-controlled period (Weeks 1-12), if patients' comorbidities for CD worsen, rescue treatment for co-morbidities should be initiated and optimized to retain the patient in the study if possible, before a decision is made to discontinue study medication.

It is suggested that the following glycemic thresholds be used for initiation or intensification of glucose-lowering therapy:

- Fasting plasma glucose > 200 mg/dL (11.1 mmol/L) from baseline to Week 6

- Fasting plasma glucose > 160 mg/dL (8.88 mmol/L) from Week 6 to Week 12.

It is suggested that certain classes of agents be used to treat co-morbidities. For the treatment of hyperglycemia, metformin should be considered first and the dose increased, if tolerated, to the maximally effective dose (i.e., ≥1500 mg daily) prior to adding another agent.

For the treatment of hypertension, ACE inhibitors should be used over diuretics known to cause hypokalemia (e.g., hydrochlorothiazide) and dose should be optimized. Mineralocorticoid receptor antagonists (e.g., spironolactone) should be used as second line agents for hypertension and to prevent hypokalemia; however the concomitant use of ACE inhibitors and spironolactone or eplerenone is prohibited. Serum potassium should be monitored closely and hypokalemia should be treated promptly if it occurs. Oral or intravenous potassium supplements can be used to treat hypokalemia, and spironolactone should be considered to prevent hypokalemia in patients with edema and/or hypertension. It is suggested that oral potassium supplementation be initiated if the serum potassium level is even mildly decreased (e.g., ≤ 3.3 mg/dL [≤ 3.3 mEq/L]), and more aggressively treated (e.g., consider intravenous potassium replacement) if the patient is symptomatic or serum potassium level falls to < 3.0 mg/dL [< 3.0 mEq/L]).

Serum lipid levels should be monitored and treated as appropriate.

Thresholds for considering discontinuation of patients from study drug or from the study are discussed in Section 7.1.4.

6.1.4 Guidelines for continuation of treatment

Osilodrostat therapy (or matching placebo) is continued unless it must be interrupted or discontinued for safety or other reasons. See Section 6.3 ‘Dose modifications’ for details.

6.1.5 Treatment duration

The treatment duration is 48 weeks in the Core study (Periods 1 and 2), and up to an additional 48 weeks for patients who agree to continue on the optional extension phase. Patients may continue treatment with the study drug until unacceptable toxicity has been experienced, and/or treatment is discontinued at the discretion of the investigator or withdrawal of consent. In the absence of study drug discontinuation, patients will receive osilodrostat for a minimum of 36 weeks to a maximum of 48 weeks during the Core phase.

The optional extension phase will end when all patients who were eligible have transitioned into the long-term safety follow-up study, or were discontinued from the study. Patients must end participation in the optional extension phase within 4 weeks after Protocol Amendment 02 is approved at the site, or by Week 96, whichever occurs first. Patients participating in the optional extension phase between Week 48 and Week 72, and who are eligible, should transition into the long-term safety follow-up study at the next study visit. Patients participating in the optional extension phase between Week 72 and Week 96, and who are eligible, should transition into the long-term safety follow-up study within 4 weeks, at an unscheduled visit if needed, of Protocol Amendment 02 approval at the site.

6.2 Dose titration guidelines

6.2.1 Study Period 1: The double-blind, placebo-controlled period (Weeks 1-12).

For patients on osilodrostat arm, the IE is responsible for study drug dose titrations during Period 1, as the Investigators will not have access to UFC, serum cortisol, and other related laboratory results (as described in Section 4.1) that could disclose the randomized treatment assignment. The IE will determine the study drug dose once the mUFC level is available from scheduled study visits at Week 2, Week 5 and Week 8, and has access to following data:

- treatment allocation
- mUFC and individual 24-hour UFC values from the most recent study visit (see Table 7-1a), and mUFC values since the beginning of the trial (as reported by the central laboratory)
- other relevant laboratory data (i.e., serum cortisol, ACTH, and chemistry)
- data on the presence or absence of clinical signs and symptoms of adrenal insufficiency (AI; as recorded on the clinical signs and symptoms of AI eCRF page from the most recent study visit) (see Section 7.2.2.1.1 for details).
- vital signs as recorded in the eCRF
- study drug doses since the beginning of the trial (as recorded on the Drug Administration Record (DAR) eCRF).

In order to maintain the study blind, communication from the IE to the investigator must be limited to communication of study drug dose decisions through the IRT system.

For patients in the placebo arm, a simulated dose titration sequence will be used to maintain the blind.

6.2.1.1 Dose up-titration during Period 1

The initial study drug dose in Period 1 is osilodrostat or placebo 2 mg b.i.d. The dose escalation sequence is: 5 mg b.i.d., 10 mg b.i.d. and 20 mg b.i.d. The IE will up-titrate the osilodrostat dose to the next dose in the sequence, based on the mUFC value until mUFC is normalized. While the goal is to normalize mUFC, decision to up-titrate dose will take into consideration the totality of the data available on each patient e.g. level of mUFC, rate of decrease of mUFC and tolerability of study drug (see Section 6.3).

Once mUFC is in the normal range (i.e., mUFC $\leq$ ULN and $\geq$ LLN), the dose should be maintained, provided there are no safety concerns requiring a dose reduction or interruption (as described below and in Section 6.3).

6.2.1.2 Dose down-titration during Period 1

The dose of study drug may be down-titrated or interrupted by the IE in patients with mUFC values < LLN or close to LLN together with signs and/or symptoms of adrenal insufficiency. However, it is expected that the investigator will take immediate action to temporarily withhold study medication, without waiting for instructions from the IE, if their patient had suspected adrenal insufficiency, or any AE that requires replacement therapy with glucocorticoids (see

Section 6.3.1 for details). In the event the investigator interrupts study drug, this information must be recorded in the eCRF as soon as possible, so that the IE can take this into account when selecting the next scheduled study drug dose.

6.2.1.3 Intermediate doses for dose adjustment

The preferred doses for either up or down-titration are the standard recommended doses of 2, 5, 10 and 20 mg b.i.d. during Period 1. The preferred intermediate doses are: 3, 7, and 15 mg b.i.d., but other doses may be selected if necessary.

Examples of the appropriate use of intermediate study drug doses are described below:

- A patient previously down titrated from a higher dose for signs and symptoms of adrenal insufficiency to the next lower standard dose (e.g., down titrated from 10 mg b.i.d. to 5 mg b.i.d.), and who experienced an increase in mUFC > ULN, or developed signs and symptoms of hypercortisolism at the lower dose, may be up titrated to an intermediate dose (e.g. 7 mg b.i.d., or, if needed, another intermediate dose between 5 mg and 10 mg b.i.d.) to optimize control.
- A patient who had mUFC > ULN, with or without signs and symptoms of hypercortisolism at one dose, and subsequently had mUFC < LLN or close to the LLN, accompanied by signs and symptoms of hypocortisolism at the next standard higher dose (e.g., after up-titration from 5 mg b.i.d. to 10 mg b.i.d.) may be down titrated to an intermediate dose (e.g., 7 mg b.i.d., or, if needed, other doses between 5 mg and 10 mg b.i.d.) to optimize control.

In patients treated with either osilodrostat or placebo, the study drug could be down-titrated to a dose lower than 2 mg b.i.d., if indicated. In addition, doses of 1 mg b.i.d. or lower can be used, e.g., 1 mg q.d. or 1mg q.o.d. (every other day), if needed for patients that are sensitive to osilodrostat. Importantly, only placebo-treated patients with mUFC < 1.5 x ULN will be down-titrated to doses below 2 mg b.i.d., to avoid unblinding and prolonged hypercortisolism after the Week 12 visit for patients with severely uncontrolled hypercortisolism.

The IEs, investigators, and other site staff should be aware that the use of non-standard doses increases the complexity of dispensing drug to the patient, and self-administration of drug by the patient (see Section 6.6 for details).

6.2.1.4 Communication and implementation of dose changes

As soon as possible (e.g. within 48 hours, if feasible) after the receipt of UFC values for each patient:

1. The IE must determine the next study drug dose (as described in the dosing guidelines, above)
2. The IE must communicate the dose decision for each patient to the corresponding site, through the IRT system in a blinded manner.
3. If a dose change is needed and can be accommodated with the patients' current supplies, the IRT system will provide instructions for the new dose, with the option for this dose change communication to be either via the phone or during an unscheduled visit (per investigator judgment). If a different tablet strength is needed to implement the dose change, the IRT system will recommend that the patient returns to the site (unscheduled

visit) for a dose change. The following need to be completed during both at scheduled and unscheduled site visits:

a. Patients should return all unused tablets to the site for drug accountability
b. Patients will receive adequate quantities of medication at the new dose to last until the next scheduled visit.
c. Patients must receive written instructions regarding the new dose and dosing schedule.

Phone contact: Sites should also initiate a patient contact via the phone approximately 2-5 days after a visit, regardless of whether a dose change was made to assess the following:

1. verify the dose the patient is taking
2. assess the presence or absence of signs and symptoms of adrenal insufficiency or glucocorticoid withdrawal.

Note: If the dose is maintained without change, the patient does not need to return to the site until the next scheduled study visit.

As a general rule, the patient must be on a dose of study medication for at least 4 days before starting a UFC sample collection, in order to ensure that the UFC results reflect adequate exposure to the dose. Therefore, if the time interval between availability of the new dose and next scheduled visit is less than 6 days (when 2 x 24-hour urine collections are required for dose titration) or 7 days (when 3 x 24-hour urine collections are required, e.g. Week 12 visit), patients should not be requested to change their dose until the next scheduled visit when new dosing instructions will be provided and study drug dispensed.

The above guidance is not applicable when urgent dose changes need to be made to ensure patient safety. All study drug dose changes must be documented in the eCRF.

6.2.2 Study Period 2: The single-arm, open-label dose titration period (Weeks 12-48)

Immediately after the Week 12 visit, all patients (in both treatment groups) will receive open-label osilodrostat (as described in Section 4.1).

Investigators will up-titrate osilodrostat doses to achieve mUFC normalization, according to 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 then 30 mg b.i.d.. For any patients on less than 2 mg b.i.d. at the beginning of Period 2, the investigator can increase the dose to 2 mg b.i.d. when the results of the Week 14 visit are available, and then follow the above dose escalation sequence as needed to normalize mUFC. The investigator will follow the same dosing guidelines as described above for the IE (Section 6.2.1: Study Period 1).

The investigator must remain vigilant to signs and symptoms of adrenal insufficiency and glucocorticoid withdrawal between Week 12 and receipt of the Week 14 UFC results and take appropriate action with regard to the osilodrostat dose, if needed. An unscheduled visit during this time may facilitate assessment of the patient.

Osilodrostat treatment continues until the Week 48 visit with dose-titration to the minimum effective dose that maintains UFC ≤ULN. This dose is continued unless a change is required based on mUFC results, or an AE occurs that requires dose reduction or temporarily

withholding osilodrostat. Dose adjustments are to be performed by the investigator as described in the dosing guidelines above for the IE (Section 6.2.1: Study Period 1).

6.2.3 Extension phase (Weeks 48 - 96):

Osilodrostat treatment continues for up to 48 weeks at the established effective dose unless a change is required based on mUFC results, or an AE occurs that requires dose reduction or temporarily withholding osilodrostat. Dose adjustments are to be performed as described for Period 2.

Patients who continue to benefit from treatment during the optional extension phase, have the option to continue treatment on study until any of the following occurs:

a) they no longer benefit from treatment or
b) managed access program becomes locally available or
c) an alternative treatment option becomes locally available or
d) within 4 weeks after Protocol Amendment 02 is approved at the site, since a separate long term follow up study is now available or by Week 96, whichever comes first. Refer to Section 6.1.5 for details

For patients who transition into a separate long-term study or managed access program, the EOS (last dose + 30 days) visit is not applicable, as treatment on osilodrostat will not be interrupted, and only the EOT visit will be performed.

Those patients who will not continue treatment will complete the EOT extension visit and an EOS (last dose + 30 days) visit, for details of assessments, please refer to Section 7.1.4.

6.3 Dose modifications

6.3.1 Dose modification and dose delay

Please refer to Section 4.1 “Description of study design” and Section 6.2 “Dose titration guidelines” for further information about dose and dosing regimen during various periods of the trial.

In the event of a major safety issue, the investigator may order any laboratory, radiology, or other diagnostic testing required in the safety assessment. In the case of suspected acute adrenal insufficiency or adrenal crisis, the investigator may order and see the results of an urgent serum cortisol level during the double-blind phase of the trial (Weeks 1-12). However, since knowledge of the serum cortisol level could, in effect, unblind the investigator, this action should be reserved for situations in which the clinical diagnosis is in doubt, and the serum cortisol level is considered necessary in the evaluation and treatment of the patient.

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study drug. The following guidelines (Table 6-1 and Table 6-2) need to be applied. These changes must be recorded in the eCRFs.

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

Toxicity	Suggested actions	
	From Week 1 to 12 The investigator must immediately inform the IE about AEs and actions taken with study drug by completing the appropriate eCRF.	**From Week 12 Onward**
Symptomatic adrenal insufficiency See Section 6.3.2 for additional detail.	If the investigator at any time suspects adrenal insufficiency, they can immediately interrupt study drug and initiate replacement with glucocorticoids. Upon recovery as assessed by the investigator*, glucocorticoid therapy can be tapered as tolerated, and study drug can be re-started. The decision to restart study drug will be made by the investigator. The AE and associated treatments with changes to study drug need to be appropriately documented in the eCRF. *Recovery is assessed clinically by the investigator. A general guideline is that glucocorticoid taper can begin when 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 mUFC is normal or > ULN. The IE can adjust the dose when sufficient information is provided, i.e., serum cortisol, one or more (up to three) 24-hour UFC result, plasma glucose and electrolytes (as central lab assessment) and completed eCRF pages with clinical signs and symptoms associated with hypocortisolism/adrenal insufficiency event.	
Persistent asymptomatic hypocortisolism (mUFC < LLN) at the lowest dose of osilodrostat (1 mg every other day) See Section 6.3.2 for additional detail.	The IE can interrupt study drug and restart at the same dose as clinically indicated (based on information in the eCRF).	The investigator can interrupt study drug and restart at the same dose as clinically indicated.
Glucocorticoid withdrawal syndrome See Section 6.3.2 for additional detail.	The investigator can interrupt dose until withdrawal symptoms have improved.	The investigator can reduce or interrupt dose until withdrawal symptoms have improved.
*Hypotension (mild, reversible)	The investigator can interrupt dose until blood pressure levels have improved.	The investigator can reduce or interrupt dose until blood pressure levels have improved.
*Hypertension	The investigator can interrupt dose until blood pressure levels have 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.**	The investigator can reduce or interrupt dose until blood pressure levels have 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	The investigator can interrupt dose until improved; consider spironolactone for treatment of edema.	The investigator can reduce or interrupt dose until improved; consider spironolactone for treatment of edema.
*Hypokalemia	The investigator can interrupt dose until improved; replace potassium; consider spironolactone or eplerenone for prevention and treatment of hypokalemia	The investigator can reduce or interrupt dose until improved; replace potassium; consider spironolactone or eplerenone for prevention and treatment of hypokalemia

Toxicity	Suggested actions	
	From Week 1 to 12 The investigator must immediately inform the IE about AEs and actions taken with study drug by completing the appropriate eCRF.	**From Week 12 Onward**
*Hyperkalemia	The investigator can interrupt dose until improved; if on spironolactone or eplerenone, reduce or interrupt; treat with kayexalate and other potassium lowering therapies as needed.	The investigator can reduce or interrupt dose until improved; if on spironolactone or eplerenone, reduce or interrupt; treat with kayexalate and other potassium lowering therapies as needed.
*Hirsutism (women only)	The investigator can interrupt dose until improved; review testosterone level; consider treatment with spironolactone, cyproterone acetate or finasteride per local guidelines	The investigator can reduce or interrupt dose until improved; review testosterone level; consider treatment with spironolactone, cyproterone acetate or finasteride per local guidelines
*Acne (women or men)	The investigator can interrupt dose until improved; review testosterone level; consider treatment with spironolactone, cyproterone acetate or finasteride per local guidelines	The investigator can reduce or interrupt dose until improved; review testosterone level; consider spironolactone, cyproterone acetate or finasteride per local guidelines
* Treatment of co-morbidities should be optimized during the screening period and may be considered in these situations and throughout the study treatment period (see Section 6.1.3 for details).		

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

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

Isolated total Bilirubin elevation	
> ULN – 1.5 x ULN	Maintain dose level
> 1.5 - 3.0 x ULN	Interrupt study drug dose. Monitor LFTs 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*	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. If resolved in > 14 days, then discontinue patient from study drug treatment. The patient should be monitored weekly (including LFTs[a]), or more frequently if clinically indicated, until total bilirubin has returned to baseline or stabilized over 4 weeks.
> 10.0 x ULN*	Discontinue patient from study drug treatment The patient should be monitored weekly (including LFTs[a]), or more frequently if clinically indicated, until total bilirubin has returned to baseline or stabilized over 4 weeks.
Isolated AST or ALT elevation	
> ULN - 3.0 x ULN	Maintain dose level
> 3.0 - 5.0 x ULN	Maintain dose level. Repeat LFTs[a] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs[a] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN
> 5.0 - 10.0 x ULN	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 If not resolved after 4 weeks, discontinue patient from study drug
> 10.0 - 20.0 x ULN	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 x ULN. Then restart study drug and decrease dose by one level. If not resolved after 4 weeks, discontinue patient from study drug
> 20.0 x ULN	Discontinue patient from study drug treatment. 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 returned to baseline or stabilized over 4 weeks.
Combined [b, c] elevations of AST or ALT and total bilirubin	
For patients with normal baseline ALT and AST and total bilirubin value: AST or ALT >3.0 x ULN combined with total bilirubin >2.0 x ULN without evidence of cholestasis[c] OR For patients with elevated baseline AST or ALT or total bilirubin value: [AST or ALT>2x baseline AND > 3.0 xULN] OR [AST or ALT > 8.0 xULN], combined with [total bilirubin >2x baseline AND >2.0 xULN	Permanently discontinue patient from study drug treatment. Repeat as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs[a]), or more frequently if clinically indicated, until AST, ALT, or bilirubin have returned to baseline or stabilized over 4 weeks. Refer to Section 6.3.3.1 for additional follow-up evaluations as applicable.

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 (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 (>2xULN and R value (ALT/ALP in x ULN) < 2).

Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values.
It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury

* Note: If total bilirubin > 3.0 x ULN is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level and continue treatment at the discretion of the investigator.

In addition, any AE per investigator judgment, regardless of suspected drug causality, may require interruption of study drug and replacement therapy with glucocorticoids until improvement of the event. These events, associated treatments along with changes to the dosing regimen of study drug need to be documented in the eCRF as soon as possible to enable the IE (up to Week 12) to make the appropriate dose decisions.

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

6.3.2 Guidance for evaluation and management of hypocortisolism

Patients with Cushing's disease treated with osilodrostat may experience a broad range of symptoms, signs, and/or lab abnormalities associated with relative or absolute hypocortisolism. Glucocorticoid withdrawal syndrome may occur with the rapid fall of cortisol levels, even while the patient's serum and/or urine cortisol levels are normal or elevated. Patients may also present with serum and/or urine cortisol levels that are below normal or in the lower part of the normal range, in the absence of symptoms. Non-specific symptoms that may be suggestive of hypocortisolism or glucocorticoid withdrawal are described in Section 7.2.2.1.1.

In patients suspected to have adrenal insufficiency, treatment with replacement or stress doses of glucocorticoids should be initiated as soon as possible as clinically indicated and consistent with local treatment guidelines.

In the event of suspected hypocortisolism or adrenal insufficiency during the period 1, the site should instruct the patient to collect one or more (up to three) 24-hour urine samples for UFC assessment and come to the site for tests for serum cortisol, plasma glucose and electrolytes (sodium and potassium). These samples should be sent to central laboratory immediately to allow the appropriate dose modification by IE. Physical exam is recommended and record of abnormal findings to the CRF.

6.3.3 Follow-up for toxicities

Table 6-1 and Table 6-2 outline the follow-up evaluation recommended for toxicities of specific types.

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

Transaminase increase combined with 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.

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 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 (Section 7.2.2.6 and Section 7.2.2.7).

6.3.4 Anticipated risks and safety concerns of the study drug

Many of the anticipated drug-related safety concerns and recommendations for actions are reviewed in Section 6.3.1 "Dose modification and dose delay."

In case of placebo treatment it is possible that patients will present symptoms related to high cortisol.

Additional anticipated risks are summarized in Section 8.1.3 "Adverse events of special interest."

For a comprehensive review of safety, see 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 must be listed on the Concomitant medications/Significant non-drug therapies after start of study eCRF.

All prescription medications and over-the-counter drugs taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Prior and Concomitant Medications page of the eCRF. 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.

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

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

Spironolactone, cyproterone acetate or finasteride for the prevention and/or treatment of hirsutism are approved in some countries and are not prohibited in this study. ACE inhibitors can be used for the treatment of hypertension, but cannot be used concomitantly with spironolactone or eplerenone.

6.4.2 Permitted concomitant therapy requiring caution and/or action

Medications that are metabolized by CYP450 enzymes

The clinical inhibitory potential of osilodrostat on CYP450 enzymes was assessed with a drug-drug interaction study using a cocktail of CYP1A2, CYP2C19, CYP2D6, and CYP3A4/5 probe substrates (caffeine, omeprazole, dextromethorphan, and midazolam respectively). Results

showed that at a single dose of 50 mg, which covers the maximum extent of interaction of 30 mg b.i.d., osilodrostat is 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).

In addition, *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 these enzymes.

Therefore concomitant medications that are known substrates of these enzymes (see Appendix 1) 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' judgment.

6.4.3 Prohibited concomitant therapy

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

- Other drug treatments for Cushing's disease;
- Medications with a "known risk to cause Torsades des Pointes (TdP)" and "possible risk to cause TdP"
- Eplerenone and glucocorticoids, except under certain conditions:
    - Eplerenone may be used if necessary in acute post-myocardial infarction management, and in the event of refractory hypokalemia in patients with hypertension or edema; glucocorticoids may be used as required for the short-term treatment of hypocortisolism or adrenal insufficiency.
- Glucocorticoids (except under certain conditions as explained below in Section 6.4.3.2).

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

Preclinical data and preliminary 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, they should be discontinued from the study.

However, if a patient requires such a drug for short-term therapy, e.g., antibiotics for active infection, then 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 2 for an e-link to a list of medications that have a "Known risk to cause TdP" and "Possible risk to cause TdP". Investigators are advised to utilize this website when considering the addition of a new concomitant medication, as the lists are periodically updated.

If necessary, a discussion can be held with the Novartis Medical Monitor when considering the use of medications with a "Known risk to cause TdP" and with a "Possible risk to cause TdP"

6.4.3.2 Glucocorticoids

Glucocorticoids may be used as required for the short-term treatment of adrenal insufficiency (See Section 6.3.2 for a detailed discussion). If glucocorticoids are used in stress doses, or as replacement therapy, for > 4 weeks, then the investigator should consider early discontinuation from osilodrostat or discontinuation from the trial.

6.5 Patient numbering, treatment assignment or randomization

6.5.1 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.

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

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

6.5.2 Treatment assignment or randomization

Eligible patients will be assigned to one of the 2 treatment arms (Section 4.1 and Section 6.1) in a ratio of 2:1 (osilodrostat: placebo respectively).

Randomization will be stratified at Day 1 according to history of pituitary irradiation (yes/no).

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the Interactive Response Technology (IRT) provider using a validated system that automates the random assignment of subject number to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication randomization list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to medication packs containing each of the study drugs.

Prior to dosing, all patients who fulfill all inclusion/exclusion criteria will be randomized via IRT to one of the 2 treatment arms. The investigator or his/her delegate will call or log on to the IRT and confirm that the patient fulfills all the inclusion/exclusion criteria. The IRT will

assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the patient. The randomization number will not be communicated to the caller.

6.5.3 Treatment blinding

Patients, investigators, other site personnel, and the Novartis Clinical Trial Team will remain blinded to the identity of the randomized treatment assignments until after the 48-week Core study database lock, using the following methods:

(1) randomization data are kept strictly confidential until the time of treatment unblinding. The bioanalyst and the pharmacokineticist will be unblinded to avoid the unnecessary analysis of placebo samples. Novartis Drug Supply Management department members will be unblinded in order to prepare the study drug supplies. The Independent Endocrinologists will have access to treatment assignment to determine dose titrations during Period 1 of the study. The DMC may also have access to treatment assignment, if needed, because they are overseeing the dose decisions of the IEs.

(2) The identity of the randomized treatment assignments will be concealed by the use of matching placebo during the randomized withdrawal period. Each dose of osilodrostat will have a matching placebo identical in packaging, labeling, schedule of administration, and appearance (color, size, and weight).

(3) The Period 1 laboratory results that could disclose the randomized treatment assignment (UFC, urine creatinine, serum and salivary cortisol, ACTH, aldosterone, renin, estradiol, estrone, androgens (testosterone, delta-4 androstenedione, DHEAS), precursors 11-deoxycortisol, 11- deoxycorticosterone)) from this period of the trial, will be kept blinded from patients, investigators and other site personnel until the 48-week Core study database lock is complete. Blinded laboratory data (e.g. UFC, serum cortisol, ACTH, etc.) will however be available to IEs responsible for dose titration during Period 1, as well as the DMC if needed.

Unblinding before database lock will only occur in the case of emergencies (Section 8.3 “Emergency unblinding”), for regulatory reporting purposes and at the conclusion of the study.

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(s) will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

Study drug use in this study includes 1 mg, 5 mg, 10 mg and (depending on availability) 20 mg tablets and matching placebo tablets. There is a unique size and color for each tablet strength (see Figure 6-1). Study drug is dispensed in a unique set of kits (bottles) for each patient at each visit. Osilodrostat (or matching placebo) is dispensed in separate bottles for each tablet 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 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 IRT system ensures that enough study drug is dispensed to treat the patient until the next scheduled visit by specifying the unique set of kits (bottles) for each patient at each visit. A minimal number of strengths will be dispensed at any one visit, as feasible.

At each study visit during Period 1 (Weeks 1-12), Period 2 (Weeks 12-48) and in Extension, the site will contact Interactive Response Technology (IRT) for identification of the specific drug supply to be used by the patient until the following visit. IRT will provide the site with study drug kit number(s) specific to the patient and the visit. For dose changes, IRT will indicate if a patient visit to the site is needed to collect study drug supplies to implement the dose change or if it may be implemented via a phone contact. 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 pharmacist 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 drugs	Dispensing	Preparation
Osilodrostat (LCI699) or placebo (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/placebo will be supplied as film coated tablets packaged in bottles.

The study medication packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the treatment arms and a dose. Responsible site personnel will identify the study drug package(s) to dispense to the patient by using the IRT and obtaining the medication number(s). Site personnel will add the subject number onto the label. Immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique subject number.

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

Table 6-4 Packaging and labeling

Study drugs	Packaging	Labeling (and dosing frequency)
Osilodrostat (LCI699) or placebo (1 mg, 5 mg, 10 mg and 20 mg)	Tablets in bottles with labels	LCI699, LCI699/Placebo (b.i.d., o.d., once every other day)

6.6.2 Drug supply and storage

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

Table 6-5 Supply and storage of study drugs

Study drugs	Supply	Storage
Osilodrostat (LCI699) or placebo	Centrally supplied by Novartis	Refer to study drug label

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 drug 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 drug and packaging on a regular basis, at the end of the study or at the time of study drug discontinuation.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study drug, 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 7-1a, Table 7-1b and Table 7-2 list all of the assessments and indicate the visits at which they are performed with an "X" for the Core and Extension phases, respectively. Visit assessments window is ± 3 days, except for Day 1 which has a +3 day window.

All data obtained from these assessments must be supported in the patient's source documentation. The table indicates which assessments produce data to be entered into the clinical database (D) or remain in source documents only (S) ("Category" column).

No eCRF will be used as a source document.

Table 7-3, Table 7-4, Table 7-5, Table 7-6, Table 7-7, [redacted] and Table 7-11 list all of the assessments required for the collection plan for Disease and Imaging Assessment, Clinical Laboratory parameters, Imaging, ECG, PK samples, Biomarkers samples, PPD and Patient Reported Outcome, respectively.

Patients must end participation in the optional extension period within 4 weeks after Protocol Amendment 02 is approved at the site, or by Week 96, whichever occurs first.

Table 7-1a Visit evaluation schedule – Core – Period 1

	Category	Protocol Section	Screening			Core Treatment					Post-Treatment Follow-up				
			Wash-out	Post wash-out		Period 1					For patients discontinuing during Period 1				
Day			**from -56**	**up to -15**	**-14 to -1**	**1**	**15**	**36**	**57**	**85**	**15**	**36**	**57**	**85**	**Last dose +30d**
Week			**from -8**	**up to -3**	**-2 to -1**	**1**	**2**	**5**	**8**	**12**	**2**	**5**	**8**	**12**	
Obtain Informed consent	D	7.1.1	x												
IRT Contact	S		x			x	x	x	x	x				x	
IRT Randomization	S					x									
Patient history															
Demography	D	7.1.1.3	x												
Inclusion/Exclusion criteria	D	5.2 & 5.3			x										
Relevant medical history/Current medical conditions	D	7.1.1.3	x												
Cushing's Disease history	D	7.1.1.3	x												
Prior/concomitant medication	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
Body height	D	7.2.2.3	x												
Body weight and Waist Circumference	D	7.2.2.3	x			x	x	x	x	x	x	x	x	x	x
Physical features of Cushing's disease	D	7.2.1.2	x							x				x	
Signs and symptoms of adrenal insufficiency	D	7.2.2.1.1				x	x	x	x	x	x	x	x	x	x
Vital signs															
Body temperature/ Blood pressure/Pulse rate	D	7.2.2.2	x			x	x	x	x	x	x	x	x	x	x
Laboratory assessments															

	Category	Protocol Section	Screening			Core Treatment					Post-Treatment Follow-up				
			Wash-out	Post wash-out		Period 1					For patients discontinuing during Period 1				
Day			from -56	up to -15	-14 to -1	1	15	36	57	85	15	36	57	85	Last dose +30d
Week			from -8	up to -3	-2 to -1	1	2	5	8	12	2	5	8	12	
Hematology	D	7.2.2.4.1		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
Thyroid Panel, FSH	D	7.2.2.4.5		x		x		x		x		x		x	
LH	D	7.2.2.4.7				x		x		x		x		x	
Coagulation	D	7.2.2.4.4				x				x				x	
Urinalysis	D	7.2.2.4.3				x	x	x	x	x	x	x	x	x	x
Pregnancy test (serum)	D	7.2.2.4.8		x											
Pregnancy test (urine)	D	7.2.2.4.8				x	x	x	x	x	x	x	x	x	x
Efficacy Assessment															
24-hour Urinary Free Cortisol and creatinine	D	7.2.1.1		x		x	x	x	x	x	x	x	x	x	x
Serum testosterone and estradiol	D	7.2.2.4.6				x	x		x	x	x		x	x	x
Plasma ACTH and serum cortisol	D	7.2.2.4.6			x	x	x	x	x	x	x	x	x	x	x
Serum aldosterone and serum 11-deoxycortisol	D	7.2.2.4.6				x	x	x	x	x	x	x	x	x	x
Serum Androstenedione, DHEAS, Estrone	D	7.2.2.4.6				x	x		x	x	x		x	x	x
Plasma Renin	D	7.2.2.4.6				x	x		x	x	x		x	x	x
Salivary Cortisol (morning and late night)	D	7.2.2.4.6		x		x	x	x	x	x	x	x	x	x	x
Serum 11-Deoxycorticosterone	D	7.2.2.4.6				x	x	x	x	x	x	x	x	x	x
Fasting serum Insulin, plasma glucose and lipids	D	7.2.2.4.7				x			x	x			x	x	x

	Category	Protocol Section	Screening			Core Treatment					Post-Treatment Follow-up				
			Wash-out	Post wash-out		Period 1					For patients discontinuing during Period 1				
Day			**from -56**	**up to -15**	**-14 to -1**	**1**	**15**	**36**	**57**	**85**	**15**	**36**	**57**	**85**	**Last dose +30d**
Week			**from -8**	**up to -3**	**-2 to -1**	**1**	**2**	**5**	**8**	**12**	**2**	**5**	**8**	**12**	
HbA1C	D	7.2.2.4.7		x		x			x	x			x	x	x

	Category	Protocol Section	Screening			Core Treatment					Post-Treatment Follow-up				
			Wash-out	Post wash-out		Period 1					For patients discontinuing during Period 1				
Day			from -56	up to -15	-14 to -1	1	15	36	57	85	15	36	57	85	Last dose +30d
Week			from -8	up to -3	-2 to -1	1	2	5	8	12	2	5	8	12	
Safety															
Adverse Events	D	8.1				As required									
12 Lead safety ECG assessment	D	7.2.2.6.2		x	x	x	x	x	x	x	x	x	x	x	x
12-Lead 24-hour Holter ECG recording	D	7.2.2.6.1			x		x			x	x			x	
Biomarkers															
[redacted]															
Hair Cortisol	D	7.2.4.2				x									
[redacted]															
Imaging															
Pituitary MRI (or CT)	D	7.2.2.5	x												
DXA scan	D	7.2.1.3	x												
Patient Reported Outcomes															
C-SSRS	D	7.2.6		x		x	x	x	x	x	x	x	x	x	x
Cushing QoL	D	7.2.6				x	x	x	x	x	x	x	x	x	x
Beck Depression Inventory	D	7.2.6				x	x	x	x	x	x	x	x	x	x
EQ-5D-5L	D	7.2.6				x				x				x	x
Patient diary	S	7.1.3	x			x	x	x	x	x	x	x	x	x	x
Study Drug administration	D	6.1				continuous b.i.d. dosing									
Phone contact	S	6.2.1.4				x	x	x	x	x					

	Category	Protocol Section	Screening			Core Treatment					Post-Treatment Follow-up				
			Wash-out	Post wash-out		Period 1					For patients discontinuing during Period 1				
Day			**from -56**	**up to -15**	**-14 to -1**	**1**	**15**	**36**	**57**	**85**	**15**	**36**	**57**	**85**	**Last dose +30d**
Week			**from -8**	**up to -3**	**-2 to -1**	**1**	**2**	**5**	**8**	**12**	**2**	**5**	**8**	**12**	
PK sampling	D	7.2.3				x	x	x	x	x					
End of Phase disposition	D				x									x	

Table 7-1b Visit evaluation schedule– Core (continued) – Period 2

	Category	Protocol Section	Core Treatment											Post-Treatment Follow-up
			Period 2										EOT Core	All Patients
Day			**99**	**120**	**141**	**162**	**183**	**204**	**225**	**253**	**281**	**309**	**337**	**Last dose +30d**
Week			**14**	**17**	**20**	**23**	**26**	**29**	**32**	**36**	**40**	**44**	**48**	
IRT Contact	S		x	x	x	x	x	x	x	x	x	x	x	
Patient history														
Prior/concomitant medication	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
Body weight and Waist Circumference	D	7.2.2.3	x	x	x	x	x	x	x	x	x	x	x	x
Physical features of Cushing's disease	D	7.2.1.2					x			x			x	
Signs and symptoms of adrenal insufficiency	D	7.2.2.1.1	x	x	x	x	x	x	x	x	x	x	x	x
Vital signs														
Body temperature/ Blood pressure/Pulse rate	D	7.2.2.2	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
Chemistry	D	7.2.2.4.2	x	x	x	x	x	x	x	x	x	x	x	x
Thyroid Panel, FSH	D	7.2.2.4.5	x		x		x			x			x	
LH	D	7.2.2.4.7	x		x		x			x			x	
Coagulation	D	7.2.2.4.4	x		x		x			x			x	
Urinalysis	D	7.2.2.4.3	x	x	x	x	x	x	x	x	x	x	x	x
Pregnancy test (serum)	D	7.2.2.4.8											x	
Pregnancy test (urine)	D	7.2.2.4.8	x	x	x	x	x	x	x	x	x	x		x

	Category	Protocol Section	Core Treatment											Post-Treatment Follow-up
			Period 2										EOT Core	All Patients
Day			**99**	**120**	**141**	**162**	**183**	**204**	**225**	**253**	**281**	**309**	**337**	**Last dose +30d**
Week			**14**	**17**	**20**	**23**	**26**	**29**	**32**	**36**	**40**	**44**	**48**	
Efficacy Assessment														
24-hour Urinary Free Cortisol and creatinine	D	7.2.1.1	x	x	x	x	x	x	x	x	x	x	x	x
Serum testosterone and estradiol	D	7.2.2.4.6	x		x		x			x			x	x
Plasma ACTH and serum cortisol	D	7.2.2.4.6	x	x	x	x	x	x	x	x	x	x	x	x
Serum aldosterone and serum 11-deoxycortisol	D	7.2.2.4.6	x		x		x			x			x	x
Serum Androstenedione, DHEAS, Estrone	D	7.2.2.4.6	x		x		x			x			x	x
Plasma Renin	D	7.2.2.4.6	x		x		x			x			x	x
Salivary Cortisol (morning and late night)	D	7.2.2.4.6	x	x	x	x	x	x	x	x	x	x	x	x
Serum 11-Deoxycorticosterone	D	7.2.2.4.6	x		x		x			x			x	x
Fasting serum Insulin, plasma glucose and lipids	D	7.2.2.4.7	x		x		x			x			x	x
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	7.2.2.6.2	x	x	x	x	x	x	x	x	x	x	x	x
12-Lead 24-hour Holter ECG recording	D	7.2.2.6.1	x							x				
Biomarkers														
[redacted]														
Hair Cortisol	D	7.2.4.2					x						x	x

	Category	Protocol Section	Core Treatment											Post-Treatment Follow-up
			Period 2										EOT Core	All Patients
Day			**99**	**120**	**141**	**162**	**183**	**204**	**225**	**253**	**281**	**309**	**337**	**Last dose +30d**
Week			**14**	**17**	**20**	**23**	**26**	**29**	**32**	**36**	**40**	**44**	**48**	
Imaging														
Pituitary MRI (or CT)	D	7.2.2.5					x						x	
DXA scan	D	7.2.1.3											x	
Patient Reported Outcomes														
C-SSRS	D	7.2.6											x	x
Cushing QoL	D	7.2.6	x	x	x	x	x			x			x	x
Beck Depression Inventory	D	7.2.6	x	x	x	x	x			x			x	x
EQ-5D-5L	D	7.2.6	x				x			x			x	x
Patient diary	S	7.1.3	x	x	x	x	x	x	x	x	x	x	x	x
Study Drug administration	D	6.1	continuous b.i.d. dosing											
Phone contact	S	6.2.1.4	x	x	x	x	x	x	x	x				
PK sampling	D	7.2.3	x	x	x	x	x	x	x	x	x	x	x	
End of Phase disposition	D												x	x

Table 7-2 Visit evaluation schedule – Extension

	Category	Protocol Section	Extension-Treatment											Post-Treatment Follow-up
													EOT Extension	
Day			**337**	**365**	**393**	**421**	**449**	**477**	**505**	**589**	**673**	**757, then every 168 days**		**Last dose +30d**
Week			**48**	**52**	**56**	**60**	**64**	**68**	**72**	**84**	**96**	**108, then every 24 weeks**		
Obtain Informed consent	S	7.1.1	x											
IRT Contact / Drug Dispensing	S			x	x	x	x	x	x	x	x	x	x	
Prior/concomitant medication	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
Body weight and Waist Circumference	D	7.2.2.3		x	x	x	x	x	x	x	x	x	x	x
Physical features of Cushing's disease	D	7.2.1.2							x		x	x	x	
Signs and symptoms of adrenal insufficiency	D	7.2.2.1.1	x	x	x	x	x	x	x	x	x	x	x	x
Vital signs														
Body temperature / Blood pressure / Pulse rate	D	7.2.2.2		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
Chemistry	D	7.2.2.4.2		x	x	x	x	x	x	x	x	x	x	x
Thyroid Panel, FSH	D	7.2.2.4.5				x			x	x	x	x	x	
LH	D	7.2.2.4.7				x			x	x	x		x	

	Category	Protocol Section	Extension-Treatment											Post-Treatment Follow-up
													EOT Extension	
Day			**337**	**365**	**393**	**421**	**449**	**477**	**505**	**589**	**673**	**757, then every 168 days**		**Last dose +30d**
Week			**48**	**52**	**56**	**60**	**64**	**68**	**72**	**84**	**96**	**108, then every 24 weeks**		
Coagulation	D	7.2.2.4.4				x			x	x	x	x	x	
Urinalysis	D	7.2.2.4.3				x			x	x	x		x	x
Pregnancy test (serum)	D	7.2.2.4.8											x	
Pregnancy test (urine)	D	7.2.2.4.8		x	x	x	x	x	x	x	x	x		x
Efficacy Assessment														
24-hour Urinary Free Cortisol and creatinine	D	7.2.1.1				x			x	x	x	x	x	x
Serum testosterone and estradiol	D	7.2.2.4.6				x			x	x	x	x	x	x
Plasma ACTH and serum cortisol	D	7.2.2.4.6				x			x	x	x	x	x	x
Serum aldosterone and 11-deoxycortisol	D	7.2.2.4.6				x			x	x	x	x	x	x
Serum androstenedione, DHEAS, estrone	D	7.2.2.4.6				x			x	x	x	x	x	x
Plasma Renin	D	7.2.2.4.6				x			x	x	x	x	x	x
Salivary cortisol (morning and late night)	D	7.2.2.4.6				x			x	x	x	x	x	x
Serum 11-Deoxycorticosterone	D	7.2.2.4.6				x			x	x	x	x	x	x
Fasting serum Insulin, plasma glucose and lipids	D	7.2.2.4.7				x			x	x	x	x	x	x
HbA1C	D	7.2.2.4.7				x			x	x	x	x	x	x

	Category	Protocol Section	Extension-Treatment											Post-Treatment Follow-up
													EOT Extension	
Day			**337**	**365**	**393**	**421**	**449**	**477**	**505**	**589**	**673**	**757, then every 168 days**		**Last dose +30d**
Week			**48**	**52**	**56**	**60**	**64**	**68**	**72**	**84**	**96**	**108, then every 24 weeks**		
Safety														
Adverse Events	D	8.1	As required											
12 Lead safety ECG assessment	D	7.2.2.6.2	x			x			x	x	x	x	x	x
12-Lead 24-hour Holter ECG recording	D	7.2.2.6.1							x				x	
Biomarkers														
Hair Cortisol	D	7.2.4.2				x					x		x	x
Imaging														
Pituitary MRI (or CT)	D	7.2.2.5							x		x		x	
DXA scan	D	7.2.1.3									x		x	
Patient Reported Outcomes														
CushingQoL	D	7.2.6							x		x		x	x
Beck Depression Inventory	D	7.2.6							x		x		x	x
EQ-5D-5L	D	7.2.6							x				x	x
Patient diary	S	7.1.3	x	x	x	x	x	x	x	x	x	x	x	
Study Drug administration	D	6.1	continuous b.i.d. dosing											
End of Phase disposition	D												x	x

7.1.1 Screening

Written main informed consent must be obtained before any study specific assessments are performed. IRT will be contacted to register the patient at screening.

The screening assessments must be performed within 56 days before the first study drug dose on Day 1.

When applicable, patients must have undergone washout of any current drug therapy for CD according to washout periods described in the Inclusion criteria (Section 5.2). During washout, some patients may have loss of control of co-morbidities such as hypertension and diabetes. Therefore the screening period should be viewed as a "run-in" period in which the treatment of co-morbidities is optimized. Patients should be closely monitored and treated accordingly, aiming ideally for normalization of blood pressure, fasting glucose and potassium.

Information on the most recent prior medical therapy for CD will be collected including the drug name, dose, duration of therapy and outcome, provided such data are available.

The three 24-hour urine samples for the mUFC value eligibility assessment should be collected. In addition, two late night salivary cortisol samples need to be collected to exclude pseudo-cushing's disease (Alwani et al 2014). These urine and saliva samples should be collected after the washout period is over, in order to avoid any interference with the washed out therapy. It is highly recommended to send them 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 prior to Day 1.

For laboratory evaluations used to determine eligibility, repeated evaluation within the screening window is permitted for screening results out of the defined range. If laboratory results are pending at the end of the screening period, the screening period will be extended until the results become available to site. If the latest repeated laboratory result(s) meet the criteria, those results may be used to determine eligibility. If the latest repeated laboratory result(s) do not meet the criteria, the patient will be considered a screening failure.

Patients who do not meet eligibility criteria are allowed to be rescreened up to a maximum of two times. The rescreening should be documented in the source files and re-registered in IRT. If a patient is re-screened the patient should retain their study Subject Number.

If rescreening is within 60 days of the end of the original screening period, the following procedures do not have to be repeated: pituitary MRI (or CT) and DXA scan. All other assessments must be repeated.

If rescreening is done more than 60 days after the end of original screening period, all assessments must be repeated.

For details of assessments and day windows, refer to Table 7-1a.

An additional biomarker informed consent will be proposed to the patient for optional participation. For details, refer to Section 7.2.4.2.

7.1.1.1 Eligibility screening

While the investigator is responsible to ensure that each patient meets all inclusion/exclusion criteria prior to randomization, a subset of those criteria have been identified as key eligibility criteria and will also be verified by the sponsor through IRT prior to permitting the patient to be randomized. Patient's eligibility is checked in IRT. The eligibility checklist form must be completed in IRT by the investigator or designee at Day 1 prior to the patient starting the treatment phase and receiving the first dose of study drug (osilodrostat/placebo). Verification of all eligibility criteria must be done prior to contacting IRT. After the eligibility has been checked in IRT and confirmed that the patient is eligible for the trial, then the patient can be enrolled into the treatment phase of the study.

Please refer to and comply with detailed guidelines in the IRT manual.

7.1.1.2 Information to be collected on screening failures

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the Screening Phase Disposition Page.

The demographic information, informed consent and Inclusion/Exclusion pages must also be completed for Screen Failure subjects.

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 (see Section 8.2 for SAE reporting details).

If the patient fails to be randomized, the IRT must be notified within 2 days of the screen fail that the patient was not randomized.

7.1.1.3 Patient demographics and other baseline characteristics

The following patient demographics and baseline characteristics will be collected on the eCRF:

- Demography including date of birth, sex, predominant race and ethnicity (where permitted).
- Height, weight and waist circumference (see Section 7.2.2.3).
- Medical history (e.g., important medical, surgical, and allergic conditions from the patient's medical history which could have an impact on the patient's evaluation) / current medical conditions (e.g., all relevant current medical conditions which are present at the time of signing informed consent). Ongoing medical conditions, symptoms and diseases which are recorded on the Medical History eCRF should include the toxicity grade when applicable.
- Information on the most recent prior medical therapy for CD will be collected and will include information on drug, dose, duration of therapy and outcomes provided such data are available.
- Where possible, diagnoses and not symptoms will be recorded. Cushing's disease history together with the medication/treatment used will be collected.
- Prior and concomitant medications.

All assessments to be completed and documented during screening and at baseline are detailed in Table 7-1a.

Day 1 assessments / samples should be taken before the patient receives study drug as these values will be considered the baseline values for the study. Where multiple values are available for a parameter prior to study drug, the last value prior to the start of study drug will be considered the baseline value.

7.1.2 Run-in period

The screening period should be viewed as a "run-in" period in which the treatment of co-morbidities is optimized (see rescue medication plan in Section 6.1.3). For details of assessments, refer to Section 7.1.1 and Table 7-1a.

7.1.3 Treatment phase

Treatment phase is divided in 2 study periods plus an Extension phase as described in Section 4.1. Patients must be seen for all visits on the designated day with a visit window of ± 3 days for all visits, except Week 1 (Day 1) where the window is +3 days. During Period 1 (Weeks 1 to 12), patients will attend the site 2 weeks after starting study medication, and then at Weeks 5, 8 and 12.

During Period 2 (Weeks 12 to 48), patients will attend the site for the Week 14 visit, then every 3 weeks until Week 32, and every 4 weeks from Week 32 to Week 48.

At Week 48, patients have the option to enter a 48-week open-label extension phase. Patients not entering the optional Extension phase will complete the study with a 30 day follow-up.

Patients currently enrolled in the optional Extension phase must end study participation within 4 weeks after Protocol Amendment 02 is approved at the site, or by Week 96 whichever occurs first. Refer to Section 6.1.5 for details. If patients are benefitting from study treatment, they have the option to enter a separate long-term safety follow-up study or stop study treatment. Patients not entering the long-term safety follow-up study will complete the study with a 30 day follow-up.

During study treatment phases, patients will be instructed to:

- bring urine samples (collected as described in Section 7.2.1.1) to each study visit
- complete a patient diary collecting information on study drug, and urine and salivary collections. The diary will be reviewed at each site visit by site staff.

For details of assessments, please refer to Table 7-1a, Table 7-1b and Table 7-2 for the Core and Extension, respectively.

7.1.4 Discontinuation of Study drug

Patients may voluntarily discontinue from the study drug for any reason at any time. If a patient decides to discontinue from the study drug, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision while respecting the subjects rights and record this information in the patient's chart and on the appropriate eCRF pages. Patients 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 reason.

In order to help retain patients in the placebo-controlled phase (Period 1, Weeks 1 - 12), rescue therapy for co-morbid conditions should be optimized before a decision is made to discontinued patients from study drug or from the study.

Patients who discontinue study drug should NOT be considered withdrawn from the study. For patients who discontinue treatment during Weeks 1 - 12, investigators should make reasonable efforts to follow patients and perform all assessments identified for all visits up to and including Week 12 as indicated in Table 7-1a (Post-treatment follow-up) and Section 7.1.6, even if study drug has been discontinued and alternative cortisol-lowering therapy has been initiated. Patients discontinuing study drug at any time before Week 48 of the Core phase or during the optional Extension phase, should be scheduled for an End of Treatment (EOT) visit as soon as possible, at which time the assessments listed for the EOT visit will be performed (Table 7-1a, Table 7-1b and Table 7-2), with the following exceptions:

- Patients discontinuing treatment prior to the Week 36 visit do not need to have an EOT DXA scan
- Patients discontinuing prior to the Week 14 visit or between the Week 26 and Week 36 visits do not need to have an EOT pituitary MRI (or CT) (i.e. scans are needed if patients discontinue within the 12 week period prior to the Week 26 and Week 48 visits).

The date and reason for stopping the study drug should be recorded in the eCRF. If a patient fails to return for the assessments for unknown reasons, reasonable efforts (e.g. telephone, email, letter) should be made to contact them as specified in Section 7.1.7.

The investigator must discontinue study drug for a given patient if he/she believes that continuation would be detrimental to the patient's well-being. The investigator must also contact the IRT to register the patient's discontinuation from study drug.

Patients must discontinue study drug if any of the following occur:

- Emergence of the following adverse events:
- hypertension defined as office mean supine systolic BP > 180 mmHg or mean supine diastolic BP > 110 mmHg (confirmed and persistent*).
- 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).
  - hyperglycemia (fasting plasma glucose ≥ 15.0 mmol/L).

  * Persistent is defined as unresolved with osilodrostat dose change or after adjustments to other concomitant medications targeting the co-morbidity in question.
- Abnormal liver function as described in Table 6-2.
- Mean QTcF > 500 msec, if the QTc value is confirmed by a cardiologist (see Section 7.2.2.7).

- Mean 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 (see Section 7.2.2.7).
- Mean increase in QTcF > 30 msec from the mean baseline value at 1.5h post-first dose or the QTcF is > 480 msec at Day 1.
- QTcF increase > 60 msec from the pre-dose measurement earlier during the same visit.
- Pituitary tumor growth, if symptomatic or complicated by compression of the optic chiasm or other structures in and near the sella turcica (visual field loss, cranial nerve palsies, diplopia) and confirmed by MRI of the pituitary (see Section 7.2.2.5).
- Pregnancy.
- Use of prohibited treatment (refer to Section 6.4.3).
- Any other protocol deviation that results in a significant risk to the patient's safety.

The appropriate personnel from the site and Novartis will assess whether study drug should be discontinued for any patient whose treatment code has been broken inadvertently for any reason.

The investigator must also contact the IRT to register the patient's discontinuation from study drug within 2 days.

7.1.4.1 Replacement policy

Not applicable.

7.1.5 Withdrawal of 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 any longer, and does not want any further visits or assessments, and does not want any further study related contact.

Novartis will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be retained and analyzed at a later date (or as required by local regulations).

If a patient withdraws consent, the investigator should make reasonable effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision while respecting the subject's rights and record this information.

Study drug must be discontinued and no further assessments conducted.

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

7.1.6 Follow-up period

All patients must have safety evaluations performed approximately 30 days after the last dose of study drug. Patients who discontinue study drug before the Week 12 visit must perform scheduled post-treatment follow-up visits through and including Week 12 (±3 days) as indicated in Table 7-1a and Section 7.1.4. If the 30 day follow-up evaluations should occur at the time of a scheduled visit; any assessments common to both visits only need to be performed once.

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

7.1.7 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 eCRF.

7.2 Assessment types

7.2.1 Efficacy assessments

Table 7-3 Disease and Imaging Assessment collection plan

Procedure	Screening	During Treatment/Follow-up
24-hour urine samples to test for Urine Free Cortisol and creatinine	Mandated at screening (post washout)	Mandated for Periods 1 and 2, the optional Extension and the 30 day Post Treatment Follow-up, as detailed in Table 7-1a, Table 7-1b and Table 7-2. *Every effort should be made to collect samples for patients discontinuing treatment prior to Week 12 during Period 1 per Table 7-1a. Three 24-hour samples are to be collected at screening, Day 1, Week 12, Week 36, Week 48 and Week 12 Post-Treatment follow-up visit. Two 24-hour samples are to be collected at all other study time points.
Physical features of CD	Mandated at screening	Mandated for Periods 1 and 2, the optional Extension and the 30 day Post Treatment follow-up, as detailed in Table 7-1a, Table 7-1b and Table 7-2.
DXA scan (lumbar spine and total hip)	Mandated at screening	Mandated at End of Treatment Core and End of Treatment Extension, unless EOT occurs less than 6 months before the scheduled Week 96 visit.

* For patients who discontinued study drug during Period 1.

All urine samples will be sent to the central laboratory designated by Novartis for assessment. During Period 1, once results are available, an alert (by email or fax) will be sent to the IE. The central laboratory and the IE will ensure that the sites and Novartis remain blinded to the results.

Starting from Week 14 in Period 2, UFC results will be sent directly by the central laboratory to the investigators.

7.2.1.1 Urinary Free Cortisol

The primary efficacy parameter, Urinary Free Cortisol (UFC), will be assessed using a central laboratory. UFC will be measured in two or three 24-hour urine samples (Table 7-1a, Table 7-1b, Table 7-2, and Table 7-3). Values from the individual samples for a visit will be averaged to obtain the mean UFC (mUFC) level. Urine creatinine levels will also be measured to ensure validity of the 24-hour collection.

Throughout the study, patients will collect the 24-hour UFC samples preferably on consecutive days according to Table 7-1a, Table 7-1b, Table 7-2, and Table 7-3 and will complete the patient diary. Patients are to bring both the urine samples and the patient diary to each study visit.

Screening (post washout): Three 24-hour UFC samples must be collected (preferably on consecutive days) 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: Three 24-hour UFC samples will be collected (preferably on consecutive days) within 7 days prior to first day of treatment to serve as baseline value.

Treatment period: Patients will collect two 24-hour UFC samples preferably over the 2 consecutive days immediately prior to the each visit, i.e. the last urine sample should be collected the day prior to the site visit (collection may end on the morning of the visit) as defined in Table 7-1a and Table 7-1b for Periods 1 and 2 (Core phase), and Table 7-2 for the optional Extension phase. Patients will collect three 24-hour UFC samples preferably on consecutive days immediately prior to the Week 12, Week 36, Week 48 and Week 12 Post-treatment follow-up visits. If only one UFC value is available at a visit, this value will be used for dose decision making only and not for mUFC based analysis.

7.2.1.2 Physical features of Cushing's disease

The following clinical signs (physical findings) of Cushing's disease will be assessed clinically for severity at time points defined in Table 7-1a, Table 7-1b, Table 7-2 and Table 7-3: facial rubor, hirsutism (female only), striae, supraclavicular and dorsal fat pads, proximal muscle wasting (atrophy), central (abdominal) obesity, and ecchymoses (bruising). These clinical signs are to be rated on a semi-quantitative scale as follows: 0=absent; 1=mild; 2=moderate; and 3=severe.

Physical features of Cushing's disease will also be documented by photography. A total of four photographs will be taken. Two photographs, one frontal and one lateral from the shoulders up will be taken to assess facial plethora (rubor), supraclavicular and dorsal fat pads. Two photographs, frontal and dorsal of the trunk with patient in standing position will be taken to assess striae, proximal muscle wasting (atrophy), central (abdominal) obesity, and ecchymoses (bruising). In order to maintain confidentiality, photographs will not be published without the explicit written consent of the patient. Photographs will be centrally collected and checked for quality by an imaging vendor. The quality checks will be detailed in the vendor manual.

If for cultural reasons, usual lifestyle, or other reasons, photographic assessments cannot be performed, this must be discussed with the sponsor on a case-by-case basis and sponsor approval will be required.

7.2.1.3 Bone mineral density assessments

Bone mineral density (BMD) of the lumbar vertebrae (L1-L4) and left total hip are to be measured using Lunar or Hologic DXA (dual-energy X-ray absorptiometry; DXA) instruments. A patient should be scanned on the same DXA instrument throughout the study. If a scan of the left proximal femur is not possible, then the right proximal femur can be used which is then to be used consistently throughout the study. Patients are to be positioned and scanning is to be performed according to the manufacturer's instructions and the imaging acquisition guidelines provided for this study. The image acquisition guidelines include detailed instructions on scanning methods, calibration of individual DXA machines and cross-calibration of DXA machines at different sites. The BMD results must be reported in actual density (gm/cm^2) and standardized against the peak bone mass in a healthy young adult population (BMD T-score). Analysis and reporting of BMD results will be conducted centrally by the imaging vendor for this study. This assessment will be done as defined in Table 7-1a, Table 7-1b, Table 7-2 and Table 7-3. If EOT occurs less than 6 months before the scheduled Week 96 visit, MRI (or CT) and DXA is not mandatory at EOT.

Bone mineral density assessments will not be done in patients that are enrolled in Germany.

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing physical examination, vital signs, laboratory evaluations, radiological assessments, imaging assessments, cardiac assessments, as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 8. The risk of suicide will be also collected and assessed as part of safety monitoring.

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 pelvic exams will be performed. This will be conducted at visits according to Table 7-1a, Table 7-1b and Table 7-2.

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

7.2.2.1.1 Signs and symptoms of adrenal insufficiency

Signs and symptoms of adrenal insufficiency (AI) should be assessed at every study visit and / or contact according to Table 7-1a, Table 7-1b and Table 7-2. Signs and symptoms of AI are to be recorded on the Signs and symptoms of AI eCRF and in the AE eCRF during Period 1, and in the AE eCRF only during all other study periods.

Definition of signs and symptoms of AI (Charmandari, et al 2014):

- Symptoms: Nausea, vomiting, diarrhea, fatigue, asthenia, dizziness, syncope, decreased appetite, myalgia, arthralgia, and pyrexia
- Signs: hypotension, orthostatic hypotension, and tachycardia.

7.2.2.2 Vital Signs

Vital signs include blood pressure and pulse measurements, and body temperature will be assessed according to Table 7-1a, Table 7-1b and Table 7-2. Pulse and systolic and diastolic blood pressure will be measured using an automated validated device with an appropriately sized cuff according to the following sequence and times at each visit:

1. Supine: two separate recordings after the patient has been supine for a minimum of five minutes
2. Standing: one recording after the patient has been standing for 1 minute and another recording after the patient has been standing for 3 minutes.

These measurements will be used to assess the presence of orthostatic hypotension.

A drop in systolic blood pressure of ≥20 mmHg, or in diastolic blood pressure of ≥10 mmHg in the supine vs standing measurements, or presence of lightheadedness or dizziness is considered abnormal and should be recorded on the appropriate form (see section 7.2.2.1.1).

Vital sign assessments at screening may be repeated, if necessary, up to a maximum of 3 times.

7.2.2.3 Height and 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 7-1a, Table 7-1b and Table 7-2.

To measure 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-stretchable 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 7-4 below) are to be performed by the central laboratory.

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

Table 7-4 Central Clinical laboratory parameters

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, RBC Morphology, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands, Other (absolute value preferred , %s are acceptable)
Chemistry	Albumin, Alkaline phosphatase, ALT, AST , Bicarbonate, Glucose, Calcium, Chloride, Creatinine, Creatine phosphokinase (CPK), Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), inorganic phosphorus, lipase, amylase, magnesium, potassium, sodium, Total Bilirubin, Direct Bilirubin, Indirect Bilirubin, Total Protein, Blood Urea Nitrogen (BUN) or Urea, Uric Acid
Urinalysis	Macroscopic Panel (Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, pH, Protein, Specific Gravity)
Coagulation	International normalized ratio (INR), Activated partial thromboplastin time (APTT)
Thyroid	Free T4, Thyroid-Stimulating Hormone (TSH)
Additional tests	Pregnancy test: serum (central lab testing) / Urine dipstick pregnancy testing (local lab testing) Additional hormones: Serum testosterone, estradiol, FSH Serum DHEAS, androstenedione and estrone Plasma renin Plasma ACTH Serum aldosterone, cortisol and 11-deoxycortisol Salivary cortisol (morning and late night)* Serum 11-deoxycorticosterone LH Other parameters: Fasting serum insulin, fasting plasma glucose and fasting lipid profile (including: Total Cholesterol, LDL, HDL, Triglycerides) HbA1c Hair cortisol

* Salivary cortisol samples will be collected within the following intervals: Late night samples between 10:00 pm and 11:00 pm and morning samples between 8:00 am and 10:00 am. Late night salivary cortisol samples will be collected with each 24-hr UFC collection (or with the last two 24-hr UFC collections closest to the next visit if 3 samples are being collected), and the morning salivary cortisol sample will be collected with the last 24-hr UFC collection.

Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the [Laboratory Manual].

7.2.2.4.1 Hematology

Hematology tests are to be performed by the central laboratory according to the schedule of assessments and collection plan outlined respectively in Table 7-1a, Table 7-1b, Table 7-2, and Table 7-4.

7.2.2.4.2 Clinical chemistry

Chemistry tests are to be performed by the central laboratory according to the schedule of assessments and collection plan outlined respectively in Table 7-1a, Table 7-1b, Table 7-2, and Table 7-4.

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 7-1a, Table 7-1b, Table 7-2, and Table 7-4.

A midstream urine sample (approx. 30 mL) will be obtained, in order to avoid contamination with epithelial cells and sediments, and allow proper assessments.

A semi-quantitative "dipstick" evaluation will be performed.

7.2.2.4.4 Coagulation

Coagulation factors specified in Table 7-4 will be assessed by the central laboratory according to Table 7-1a, Table 7-1b and Table 7-2.

7.2.2.4.5 Thyroid Panel

Thyroid Panel specified in Table 7-4 will be assessed by the central laboratory according to Table 7-1a, Table 7-1b and Table 7-2.

7.2.2.4.6 Additional hormones

Additional hormones as specified in Table 7-4 will be assessed by the central laboratory according to Table 7-1a, Table 7-1b and Table 7-2.

7.2.2.4.7 Other laboratory parameters

Other laboratory parameters as specified in Table 7-4 will be assessed by the central laboratory according to Table 7-1a, Table 7-1b and Table 7-2.

7.2.2.4.8 Pregnancy and assessments of fertility

Serum pregnancy tests will be performed at screening and End of Treatment, and analyzed by the central laboratory. Urine dipstick pregnancy testing will be performed on site as indicated in Table 7-1a, Table 7-1b and Table 7-2.

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 randomized.

7.2.2.5 Radiological examinations

Table 7-5 Imaging Assessment collection plan

Procedure	Screening	During Treatment/Extension
Pituitary MRI (or CT)	Mandated at screening	Mandated, approximately every 6 months

Pituitary MRI scanning with gadolinium enhancement will be performed at visits according to Table 7-1a, Table 7-1b, Table 7-2, and Table 7-5. These will be assessed centrally by the imaging vendor to screen for pituitary enlargement either by tumor volume or maximum

dimension of tumor. If MRI scan with intravenous contrast (gadolinium) is contraindicated for a patient, then a non-contrast MRI scan should be performed. If the MRI cannot be performed at all, then a CT of the pituitary (with i.v. contrast if not contraindicated) may be performed. Regardless of imaging type, all regularly scheduled pituitary imaging will be centrally reviewed for consistency in the measurement of dimensions. The modality should remain consistent to that used at baseline unless there is a development of a contraindication. Please see the study imaging manual for further information. If EOT occurs less than 6 months before the scheduled Week 96 visit, MRI (or CT) and DXA is not mandatory at EOT.

7.2.2.6 Cardiac assessments

Cardiac monitoring will include 12-lead Safety ECGs, which are the primary assessment of safety at study visits. The 24 hour Holter assessments are not intended to provide real-time assessment of cardiac intervals and cardiac rhythm.

Table 7-6 ECG collection plan

Week	Day	Time point	ECG Type	Central or Local reading reading
Post wash-out (up to Week -3)	up to -15	Anytime	12 Lead	Local
-2 to -1	-14 to -1	Anytime	12 Lead	Local
-2 to -1	-14 to -1		24-hour Holter	Central
1	1	Pre-dose	12 Lead	Local
1, 2, 5, 8, 12, 14, 17, 20, 23, 26, 29, 32, 36, 40, 44	1, 15, 36, 57, 85, 99, 120, 141, 162, 183, 204, 225, 253, 281, 309	1.5 hours Post-dose	12 Lead	Local
48*	337*	Anytime for patients not continuing in extension	12 Lead	Local
2, 12, 14, 36	15, 85, 99, 253	Start at Pre-dose	24-hour Holter	Central
Post Treatment Follow-up week 2, 5, 8, 12**	15, 36, 57, 85**	Anytime	12 Lead	Local
Post Treatment Follow-up week 2, 12**	15, 85**	Anytime	24-hour Holter	Central
Optional Extension: 48*, 60, 72, 84, 96 and every six month afterward ***	337*, 421, 505, 589	1.5 hours Post-dose	12 Lead	Local
End of treatment extension visit		Anytime	12 Lead	Local
Optional Extension: 72	505	Start at Pre-dose	24-hour Holter	Central
End of treatment extension visit**			24-hour Holter	Central
Post Treatment Follow-up	Last dose + 30d	Anytime	12 Lead	Local
Unscheduled assessment		Anytime	12 Lead	Local

Week	Day	Time point	ECG Type	Central or Local reading reading

*Patients will have only one ECG at Week 48 (Day 337). For patients not continuing in optional extension, ECG will be performed anytime during the visit. For patients continuing in optional extension, ECG will be performed at 1.5 hours post-dose, except for EOT Ext., if applicable

**For patients who discontinued study drug during Period 1.

***The patients who have completed Week 96 prior to the completion of study will be followed every six months as per the schedule of assessments in Table 7-2 until transitioning either to a separate long-term safety follow-up study, a local alternative treatment option, or the completion of the study, whichever occurs first.

****End of treatment optional Extension visit assessment should be completed at the time the patients are transitioning either to a separate long-term safety follow-up study, a local alternative treatment option, or the completion of the study, whichever occurs first. Note: Patients end participation in the optional extension period study within 4 weeks after Protocol Amendment 02 approval at the site, or by Week 96, whichever occurs first.

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 7-1a, Table 7-1b, Table 7-2, and Table 7-6. Patients should be instructed to return their 24-hour Holter flashcards to the site at their next study visit in order to facilitate timely central reading of the Holter data.

7.2.2.6.2 Electrocardiogram (ECG)

Twelve-lead safety ECGs are collected at the study sites according to Table 7-1a, Table 7-1b , Table 7-2, and Table 7-6. At each visit when a study drug dose is administered, the safety ECG should be collected at 1.5 hours post-dose (approximately at the time of Cmax).

Twelve-lead safety ECGs are collected at the study site using ECG equipment provided by or validated 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 eCRF.

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

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

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

Record the following on the eCRF:

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

The Fridericia QT formula (QTcF) to correct for variations in heart rate must 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 must be reported on the ECG eCRF. 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
- 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.

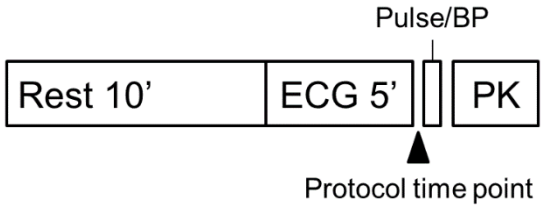
Notable ECG abnormalities must be recorded on the Adverse Events eCRF page. If there is a notable abnormality, then a cardiology consult should be obtained as soon as possible, and the Novartis Medical Monitor for this trial notified of the event.

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 assessment.

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.

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

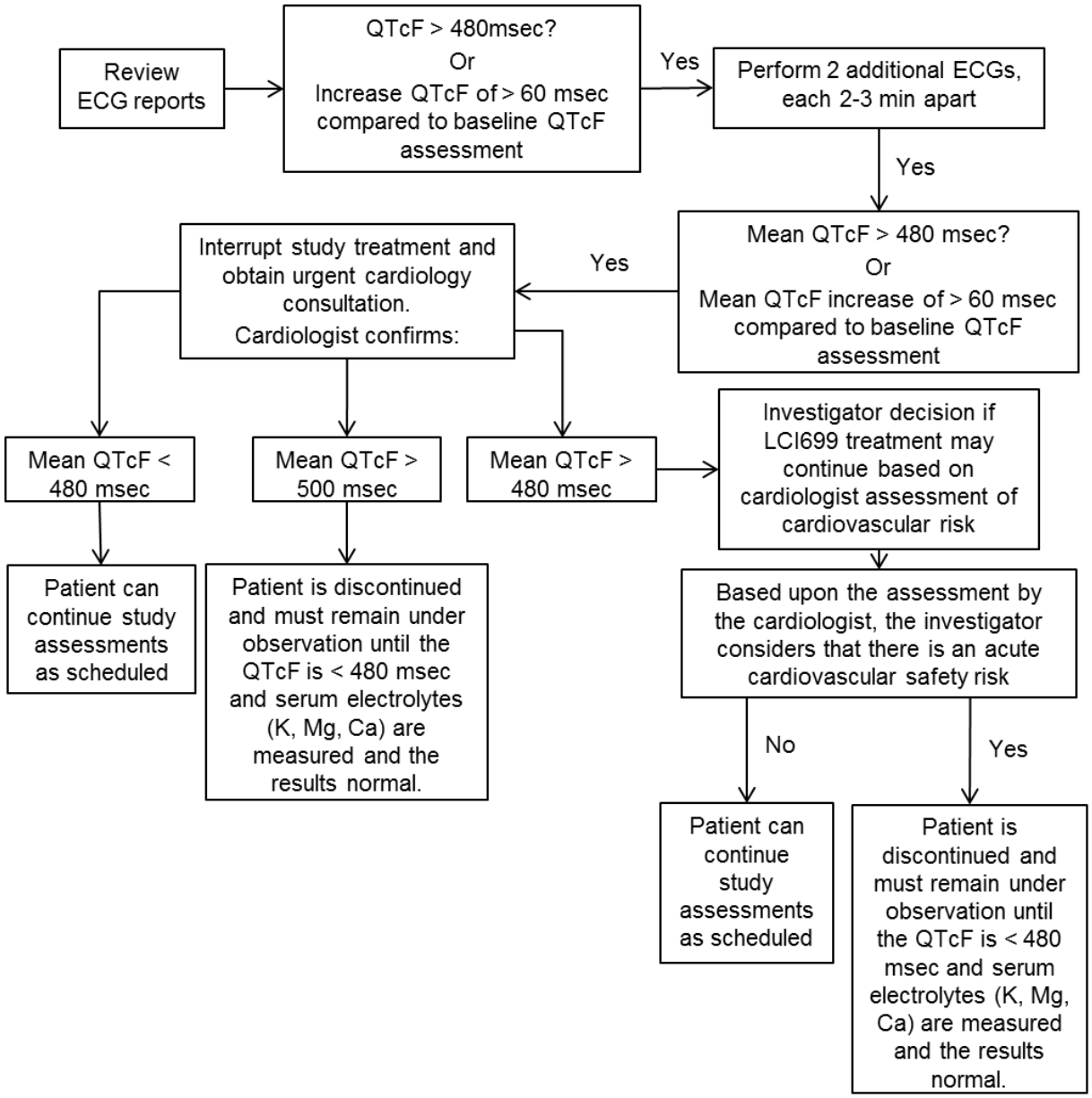
QT monitoring will occur as follows:

- 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 an increase in QTcF > 30 msec from the mean baseline value, or the QTcF is > 480 msec, then the patient must be discontinued from study. The ECG reading should be performed in triplicate (to determine a mean value) and reviewed promptly by a consulting cardiologist before discontinuing the patient from osilodrostat therapy.
- If at any following visit, a QTcF > 480 msec is observed or an increase of the QTcF of > 60 msec compared to baseline mean 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 drug 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 is to be 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.
- 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.
    - If based upon the assessment by the cardiologist, the investigator considers that there is an acute cardiovascular safety risk and that the subject should not continue with study medication, the subject needs to be discontinued immediately (discontinuation criteria described in Section 7.1.4).
    - If based upon the assessment by the cardiologist, the investigator considers that there is not an acute cardiovascular safety risk; the subject can continue to receive study medication.

Figure 7-2 QT Monitoring Flow Chart



7.2.3 Pharmacokinetics

Blood samples for osilodrostat pharmacokinetic (PK) evaluation will be collected from all patients who receive at least one dose of study drug. Pharmacokinetic blood sampling will be performed in each study period as indicated in the Visit Evaluation Schedule (Table 7-1a, Table 7-1b and Table 7-2). Time points of blood sample collection for PK analyses are outlined in Table 7-7.

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 drug dose prior to the sampling (24-h

clock time), must be obtained on all sampling days and recorded on the PK eCRF and/or Contract Research Organization (CRO) requisition form(s). Sampling problems will be noted in the relevant field in the eCRF.

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

7.2.3.1 Pharmacokinetic blood collection and handling

Complete instructions for sampling processing, handling and shipment will be provided in the [Laboratory Manual].

Blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein at specified time points described in Table 7-7. Blood will be collected into tubes containing K2-EDTA and gently inverted several times to thoroughly mix the anticoagulant. Tubes will be centrifuged to separate plasma and plasma will immediately be transferred into labeled screw-cap polypropylene, cryogenic, freezing vials (e.g. Sarstedt, part# 72.693, no skirt). Plasma samples will be placed in a freezer in an upright position until shipment on dry ice to the Novartis assigned laboratory for analysis.

Table 7-7 Pharmacokinetic blood collection log

Week	Day	Scheduled time point[a]	Dose reference ID[b]		PK Sample No.	Sample volume [mL]
1	1	Pre-dose / 0 h	1		1	Approximately 3.0
1	1	Post-dose 1 – 2 h	1		2	Approximately 3.0
2	15	Pre-dose / 0 h	2	201	3	Approximately 3.0
2	15	Post-dose 1 – 2 h	2		4	Approximately 3.0
5	36	Pre-dose / 0 h	3	301	5	Approximately 3.0
5	36	Post-dose 1 – 2 h	3		6	Approximately 3.0
8	57	Pre-dose / 0 h	4	401	7	Approximately 3.0
8	57	Post-dose 1 – 2 h	4		8	Approximately 3.0
12	85	Pre-dose / 0 h	5	501	9	Approximately 3.0
12	85	Post-dose 1 – 2 h	5		10	Approximately 3.0
14	99	Pre-dose / 0 h	6	601	11	Approximately 3.0
14	99	Post-dose 1 – 2 h	6		12	Approximately 3.0
17	120	Pre-dose / 0 h	7	701	13	Approximately 3.0
17	120	Post-dose 1 – 2 h	7		14	Approximately 3.0
20	141	Pre-dose / 0 h	8	801	15	Approximately 3.0
20	141	Post-dose 1 – 2 h	8		16	Approximately 3.0
23	162	Pre-dose / 0 h	9	901	17	Approximately 3.0

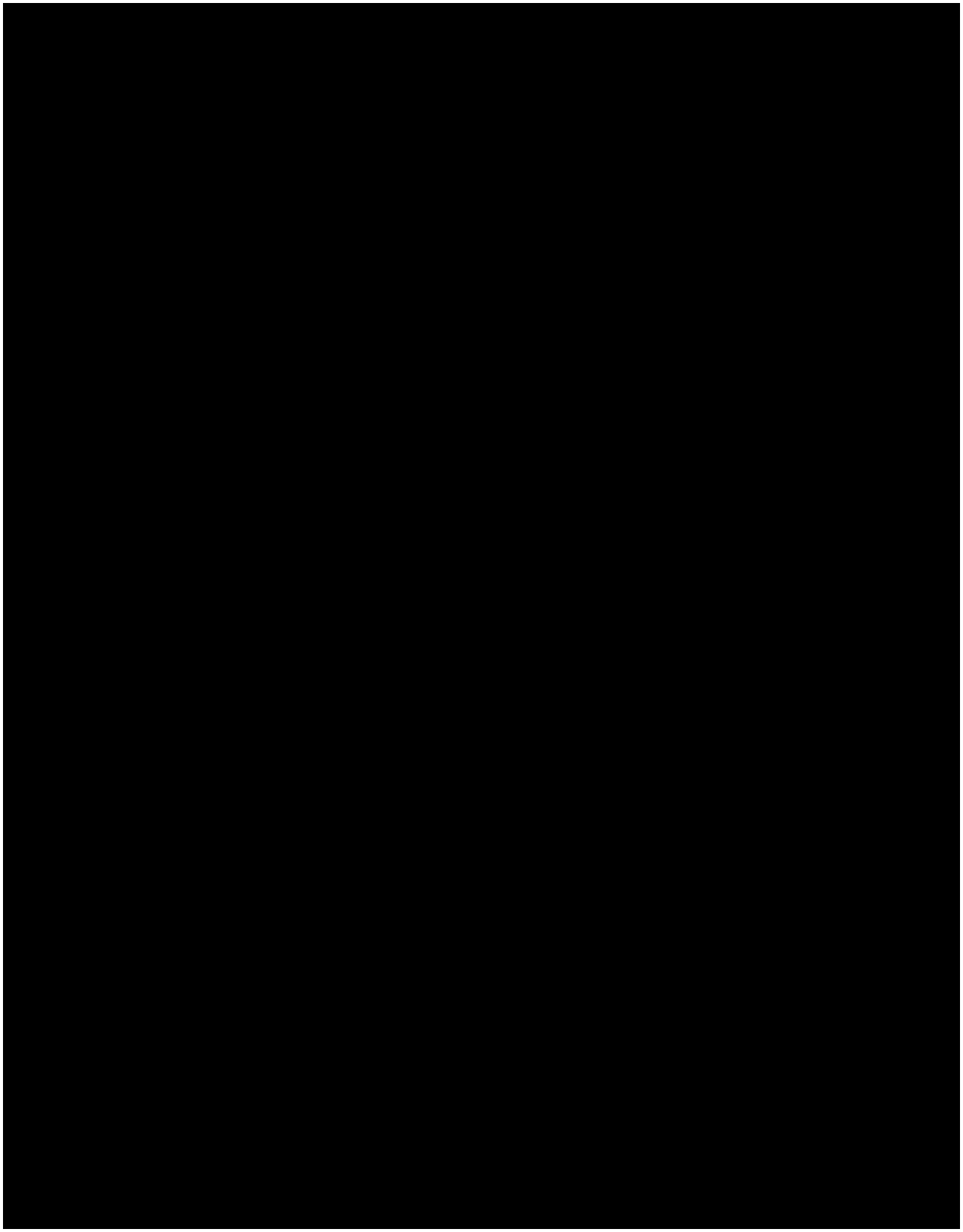
Week	Day	Scheduled time point[a]	Dose reference ID[b]		PK Sample No.	Sample volume [mL]
23	162	Post-dose 1 – 2 h	9		18	Approximately 3.0
26	183	Pre-dose / 0 h	10	1001	19	Approximately 3.0
26	183	Post-dose 1 – 2 h	10		20	Approximately 3.0
29	204	Pre-dose / 0 h	11	1101	21	Approximately 3.0
29	204	Post-dose 1 – 2 h	11		22	Approximately 3.0
32	225	Pre-dose / 0 h	12	1201	23	Approximately 3.0
36	253	Pre-dose / 0 h	13	1301	24	Approximately 3.0
40	281	Pre-dose / 0 h	14	1401	25	Approximately 3.0
44	309	Pre-dose / 0 h	15	1501	26	Approximately 3.0
48	337	12 h post dose		9801	98	Approximately 3.0
Unscheduled sample					1001+	Approximately 3.0

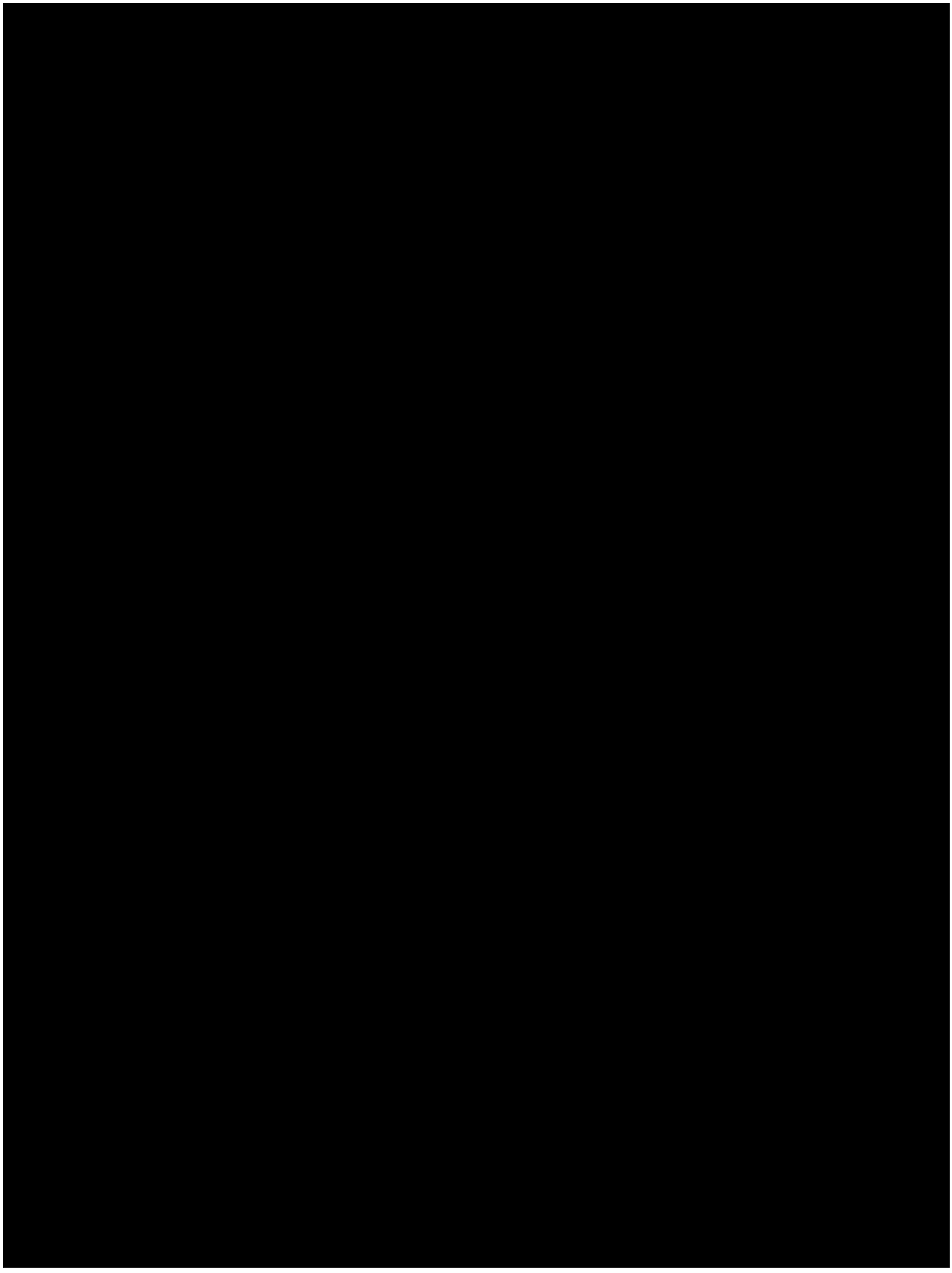
[a] The following PK assessment windows are acceptable: pre-dose sample within 0.5 h before dose administration, ±10 min for up to the 2 h timepoint, and within 0.5h before the 12h post dose sampling. If patient enters the extension phase of study, the 12 h post dose sampling should be taken prior to the first dose in the extension phase

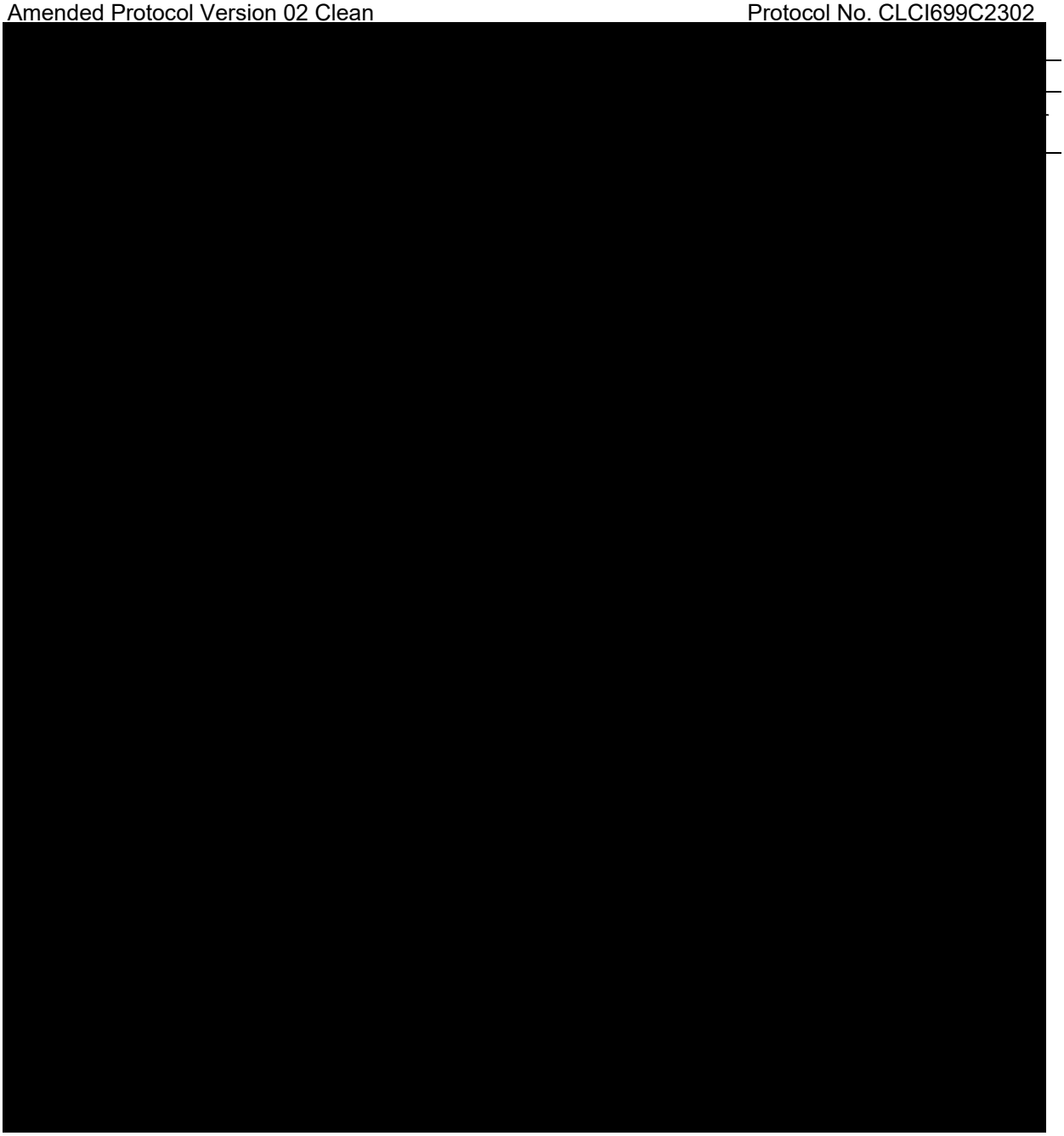
[b] For the PK pre-dose (trough) samples, the actual date and time of administration of the previous dose of study medication should also be recorded with appropriate PK collection number as indicated in the above table. The PK collection number series “1, 2, 3…” is for the osilodrostat dose administered on study visit day, while PK collection number series “201, 301, 401…” is for the previous osilodrostat dose the subject received prior to the collection of the PK pre-dose (trough) sample

7.2.3.2 Analytical method

The plasma samples from all subjects treated with osilodrostat 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). Placebo samples will not be analyzed.







7.2.5 Resource utilization

Not applicable.

7.2.6 Patient reported outcomes

Four patient reported outcome instruments will be used to assess the impact of treatment on patient quality of life and symptom burden. Patients must be asked to complete each questionnaire, including patients who discontinue from study drug, prior to clinical assessments being undertaken, and these must be completed in accordance with the schedules listed in Table 7-1a, Table 7-1b, Table 7-2 and Table 7-11. 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 must be reviewed and assessed by the investigator for responses which may indicate potential AEs or SAEs before any clinical study examinations. This assessment must be documented in study source records. If AEs or SAEs are confirmed, study investigators must 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.

Table 7-11 Patient reported outcomes (PROs) collection plan

Patient Questionnaires[1]	Week	Day	Time
C-SSRS	-5 to -1, 1, 2, 5, 8, 12, 48, and at Core Post treatment follow-up. Post treatment follow-up: Week 2**, 5**, 8**, 12**.	-35 to -1, 1, 15, 36, 57, 85, 337, Last dose +30 days. Post treatment follow-up Day 15**, 36**, 57**, 85**.	Prior to any clinical assessments, drug dosing (predose) or diagnostic testing.
CushingQoL, Beck Depression Inventory-II	1, 2, 5, 8, 12, 14, 17, 20, 23, 26, 36, 48, and at Post treatment follow-up. Post treatment follow-up Week 2**, 5**, 8**, 12**.	1, 15, 36, 57, 85, 99, 120, 141, 162, 253, 337, Last dose +30 days. Post treatment follow-up Day 15**, 36**, 57**, 85**.	Prior to any clinical assessments, drug dosing (predose) or diagnostic testing.
EQ-5D-5L	1, 12, 14, 26, 36, 48, and at Post treatment follow-up. Post treatment follow-up Week 12**.	1, 85, 99, 183, 253, 337, Last dose +30 days. Post treatment follow-up Day 85**.	Prior to any clinical assessments, drug dosing (predose) or diagnostic testing.
Cushing QoL Beck Depression Inventory-II EQ-5D-5L	Optional Treatment Extension: 72, 96, end of treatment Extension visit***, and at Post treatment follow-up.	505, 673, Last dose +30 days.	Prior to any clinical assessments, drug dosing (predose for Week 72) or diagnostic testing.

[1] Patient Questionnaires should be completed in the sequence from most specific to most general: Cushing QoL → Beck Depression Inventory-II → EQ-FD-5L

** For patients who discontinued study drug during Period 1

*** End of treatment Extension visit assessment should be completed at the time the patients transitioning either to a separate long-term safety follow-up study, a local alternative treatment option, or the completion of the study, whichever occurs first. Note: Patients to end study participation within 4 weeks after Protocol Amendment 02 is approved at the site, or by Week 96, whichever occurs first

Columbia Suicide Severity rating Scale (C-SSRS)

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a questionnaire that prospectively assesses Suicidal Ideation and Suicidal Behavior using a semi-structured interview to probe patient responses.

The **eC-SSRS** is a validated version of the C-SSRS that captures self-reported C-SSRS data via a web-based system. The eC-SSRS uses a detailed branched logic algorithm to perform the C-SSRS subject answers in order to evaluate each subject's suicidal ideation and behavior in a consistent manner. Data are handled as third party data. At the conclusion of each assessment, the investigator will receive a detailed eC-SSRS Findings Report via e-mail or fax. If the system assesses the patient as having positive suicidal signs, the investigator will be immediately notified by either fax, email and/or via telephone.

The "baseline/screening" version of the C-SSRS will be provided to patient **at the first visit** by the clinician (see Table 7-1a). This version assesses Suicidal Ideation and Suicidal Behavior during the subject's lifetime and during a predefined period. The predefined period currently used in Novartis trials is past six months for suicidal ideation and past two years for suicidal behavior. **At subsequent visits**, the "since last visit" version will be administered (see Table 7-1a, Table 7-1b).

If the score is "yes" on item 4 or item 5 of the Suicidal Ideation section of the C-SSRS or "yes" on any item of the Suicidal Behavior section, the patient must be referred to a mental health care professional for further assessment and/or treatment. The decision on whether the study drug should be discontinued is to be taken by the investigator in consultation with the mental health professional to whom the patient is referred.

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, during Study Periods 1 and 2 where it is believed that changes in Cushing's disease symptoms will occur rapidly among patients once patients stop treatment.

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.

EQ-5D-5L

The EQ-5D-5L questionnaire is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-5L is applicable to a wide range of health conditions and treatments; it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys.

The EQ-5D-5L is designed for self-completion by respondents and is ideally suited for use in postal surveys, in clinics, and in face-to-face interviews. It is cognitively undemanding, taking only a few minutes to complete.

Instructions to respondents are included in the questionnaire. The EQ-5D-5L measures 5 items on mobility, self-care, usual activities, pain/discomfort, anxiety/depression, measured on 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ-5D-5L also includes a 20 cm vertical, VAS (visual analogue scale) with on a scale of 0-100, with endpoints labeled 'the best health you can imagine' and 'the worst health you can imagine'. A single index value is analyzed for the EQ-5D-5L and VAS score.

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 eCRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's eCRF. Adverse event monitoring should be continued for at least 30 days (or 5 half-lives, whichever is longer) following the last dose of study drug. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

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

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will

not be used in this study but is collected as a seriousness criteria; rather, information about deaths will be collected though a Death form.

Table 8-1 CTCAE v4.03 - General grading guideline

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

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.
Please refer to: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

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:

- The severity grade (CTCAE Grade 1-4)
- Its duration (Start and end dates)
- Its relationship to the study drug (Reasonable possibility that AE is related: No, Yes)
- Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
- Whether medication or therapy was given
- Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)
- Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1 and which seriousness criteria have been met.

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 eCRF.

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 drug, 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 drug), should be recorded on the Adverse Events eCRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

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

8.1.3 Adverse events of special interest

Some AEs are predicted by the mechanism of action (MoA) of osilodrostat or by the underlying disease, specifically in subjects 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" are listed under the following mechanistic groups:

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

Two of the AEs of special interest, the potential for QT prolongation and 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. Preliminary clinical data suggest that there is a risk for QT prolongation in patients, at doses above the therapeutic range, but this requires further investigation to quantify the effect of osilodrostat and preliminary clinical data indicate that QT prolongation is a risk associated with osilodrostat therapy. Relevant QTc data from study [LCI699C2201] is presented in this section on the risk of QT prolongation.

[redacted]

Study [LCI699C2201]. Although the PoC study was not designed to control adequately for changes in the QT interval, locally read 12-lead EKGs were performed. In the 10-week analysis, the mean (± SD) for QTcF at screening was 388.60 ± 62.80 msec, and at the end of study was 412.31 ± 28.861msec [CLCI699C2201 PT-Listing 16.2.9-1.2.2]. No conclusion can be drawn because of the high variability of results, the absence of correlation with osilodrostat plasma concentration, and the potential for several concomitant risk factors for QT prolongation. In addition, the end of study ECGs were performed 2 weeks after the last dose of osilodrostat was administered. There were no patients with QTcB > 480 msec, and no reported QT-related AEs or cardiac arrhythmias in this POC study.

Study [LCI699C2105]. This study was 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.

8.1.3.2 Glucocorticoid withdrawal and adrenal insufficiency

Important and closely related AEs of special interest are glucocorticoid withdrawal and hypocortisolism (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 with or without symptoms of adrenal insufficiency may develop.

Although symptoms of frank adrenal insufficiency were not reported in the 10-week analysis of study [LCI699C2201], four patients did reports symptoms suggestive of glucocorticoid withdrawal. These symptoms were managed successfully by reducing the dose of osilodrostat.

8.1.3.3 Definitions and reporting

Designated events of special interest will be collected through routine AE collection. These events will be presented and discussed separately in the CSR.

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 main informed consent and until at least 30 days after the patient has stopped study drug must be reported to Novartis within 24 hours of learning of its occurrence.

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

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study drug (if there is more than one study drug), complete the SAE Report Form in English, and submit the completed form within 24 hours Novartis. Detailed instructions regarding the submission process and requirements for signatures are to be found in the investigator folder provided to each site.

A copy of the SAE data submitted must be kept with the case report form documentation at the study 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, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

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

8.3 Emergency unblinding of treatment assignment

Emergency unblinding should only be undertaken when it is essential for effective treatment of the patient. Most often, study drug discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency code breaks are performed using the IRT. When the investigator contacts the IRT to unblind a patient, he/she must provide the requested patient identifying information and confirm the necessity to unblind the patient. The investigator will then receive details of the drug treatment for the specified patient and a fax confirming this information. The system will automatically inform the Novartis monitor for the site and the Study Lead that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IRT in case of emergency. The investigator will inform the patient how to contact his/her backup in cases of emergency when he/she is unavailable. The protocol number, study drug name if available, subject number, and instructions for contacting the local Novartis CPO (or any entity to which it has delegated responsibility for emergency code breaks) will be provided to the patient in case emergency unblinding is required at a time when the investigator and backup are unavailable. However, if a mechanism is already in place to ensure that the investigator and/or back-up can always be reached in case of emergency then the procedure above is not required.

Study drug must be discontinued once emergency unblinding has occurred.

An assessment will be done by the appropriate site personnel and the Study Lead/Medical Lead after an emergency unblinding to assess whether or not study drug should be discontinued for a given patient and, if applicable, whether the patient can continue to receive study drug and be followed as described in the protocol.

8.4 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study drug 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 Drug Safety and Epidemiology Department (DS&E). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study drug any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

8.5 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.

8.6 Data Monitoring Committee

This study will institute a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will be constituted prior to the randomization of the first patient. The DMC will be responsible to review safety data at a frequency to be decided jointly by the DMC and Novartis. This includes but does not limit the role of the DMC to evaluate these data and to provide recommendations to the sponsor to continue the study without change, modify the study, or stop the study early.

It is expected that the DMC will consist of a minimum of two physicians with appropriate disease area qualifications, one cardiologist, and one statistician. There will be a meeting with the DMC describing their roles and responsibilities and discussing potential data format and process issues prior to the finalization of DMC charter.

A DMC subcommittee consisting of a group of Independent Endocrinologists (IEs) will be responsible for dose titration during the double-blind, placebo-controlled period of the study.

The DMC members who are not IEs have a responsibility to oversee the function of the IEs, specifically as it relates to reporting accurate and timely UFC information to the IEs, capturing and communicating the dose recommendation of the IE to the study sites, and showing that study drug information was actually received at the study sites.

A charter will be prepared and approved by both Novartis and the DMC. This will occur prior to the enrollment of the first patient. The DMC charter will specify the format and conduct of the meetings, conference calls, the role and responsibilities of Core and extended members, the type of data to be reviewed, and the timing and frequency of meetings.

8.7 Steering Committee

A Steering Committee (SC) will be established prior to the enrollment of the first patient. Most members will be investigators participating in the trial. Novartis representatives from the Clinical Trial Team may be present at SC meetings as non-voting participants.

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

9 Data collection and management

9.1 Data confidentiality

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

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

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

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

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and eCRFs 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 eCRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on eCRFs 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 eCRF 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 eCRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

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] samples drawn 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 and Biomarker Sample Collection eCRFs, 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, subject ID, etc.) and one copy will be retained by the site.

ECG tracings, and Imaging (MRI and DXA) will be transferred to central readers. Methods 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 is 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.

Laboratory samples for hematology, chemistry, coagulation, thyroid panel, serum pregnancy test, additional hormones and others laboratory parameters as specified in Table 7-4 will be performed by a Central Laboratory. Results of analysis tested centrally will be sent electronically to Novartis (or a designated CRO).

Samples and/or data for [redacted] PK sampling, imaging, ECG readings and IRT will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Diary data will be entered into a paper diary by the patient and brought to site at every visit for consultation by investigator.

Randomization codes and data about all study drugs dispensed to the patient and all IRT assigned dosage changes will be tracked using an Interactive Response Technology. The system will be supplied by a vendor(s), who will also manage the database. The data will be sent electronically to Novartis personnel (or designated CRO).

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

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

10 Statistical methods and data analysis

The primary analysis will be performed when all enrolled patients have completed the Core phase of study (Period 1 and 2) or have prematurely withdrawn from the study prior to the end of the Core phase. After the Core study phase, patients may continue in the optional extension phase. The additional data collected in the extension phase, will be further summarized in a final study report once these patients completed the study.

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 and approved before publication or presentation.

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

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all randomized patients who have received at least one dose of study drug (osilodrostat or placebo). According to the intent-to-treat (ITT) principle, patients will be analyzed according to the treatment and stratum they have been assigned to during the randomization. This is the default analysis set for efficacy.

10.1.2 Safety Set

The Safety Set (SS) includes all patients who received at least one dose of study drug (osilodrostat or placebo). Patients will be analyzed according to the study drug received, where treatment received is defined as the randomized/assigned treatment if the patient took at least one dose of that treatment or the first treatment received if the randomized/assigned treatment was never received.

10.1.3 Per-Protocol Set

Per-Protocol Set (PPS) consists of a subset of the patients in the FAS who are compliant with the requirements of the Clinical Study Protocol and have no CSR-reportable protocol deviation.

The criteria for CSR-reportable protocol deviation will be defined prior to database lock.

10.1.4 Pharmacokinetic analysis set

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

10.1.5 Other analysis sets

Not applicable

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data will be summarized descriptively for the FAS and the safety set (if not the same).

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

Relevant medical histories and current medical at baseline will be summarized by system organ class and preferred term, by treatment group and all patients.

10.3 Treatments (study drug, concomitant therapies, compliance)

When appropriate, patients in a given analysis set can be classified into mutually exclusive treatment arms as described below:

For patients in FAS/PPS

Osilodrostat arm: patients randomized to osilodrostat for the placebo control period of the study

Placebo arm: patients randomized to placebo for the placebo control period of the study

For patients in SS

Osilodrostat arm: patients receiving osilodrostat for the placebo control period of the study

Placebo arm: patients receiving placebo for placebo control period of the study

Exposure to study drug will be summarized descriptively using SS by treatment arm and study periods. The actual and planned doses administered and reason for dose change will be listed.

The number of patients with dose adjustments will be summarized by treatment arms, and all dosing data will be listed.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized by ATC class, preferred term, treatment arms and study periods for the safety set. The usage of concomitant medications for the treatment of hypertension, diabetes, and dyslipidemia will be separately summarized.

10.4 Primary objective

The primary objective is to demonstrate the superiority of osilodrostat compared to placebo in achieving a complete response (mUFC ≤ ULN) at week 12.

10.4.1 Variable

The primary efficacy variable is the proportion of randomized patients in each treatment arm who are complete responders at Week 12.

10.4.2 Statistical hypothesis, model, and method of analysis

The primary analysis will be based on a Cochran–Mantel–Haenszel (CMH) exact test stratified by the history of pituitary irradiation (yes/no) using the FAS. Following the ITT principle, patients are analyzed according to the drug and stratum they were assigned to at randomization.

The statistical null hypothesis states that the complete response rates at the end of the 12-week placebo-controlled period (i.e., at Week 12) are the same between the two randomized arms. To test this hypothesis, if the 1-sided p-value is ≤ 0.025, and the odds ratio (osilodrostat vs. Placebo) is > 1, the null hypothesis will be rejected and the complete response rate in the osilodrostat arm will be considered higher than that in the placebo arm.

10.4.3 Handling of missing values/censoring/discontinuations

It is scheduled to collect three individual 24 hours Urine Free Cortisol (UFC) samples at visits Weeks 1, 12, 36, 48 and Week 12 Post-treatment Follow-up, and two UFC samples at all other visits. For a given visit, Mean Urine Free Cortisol (mUFC) is the mean of all available (need to be ≥2) individual UFC values determined at a central laboratory. In case only one or no individual UFC value is available, the mUFC will be considered missing for that visit.

During the double blind period, early discontinued patients (prior to Week 12) will be followed at regular visits and have assessments performed as indicated in Table 7-1a (post-treatment

follow-up). Patients who discontinued prior to Week 12 or had a missing mUFC assessment at Week 12 will be considered as non-responder in the primary analysis. No imputation will be used.

10.4.4 Supportive and sensitivity analyses

As a supportive analysis to the primary analysis, an un-stratified Fisher's exact test of the primary endpoint will be performed using FAS.

In addition, both stratified CMH exact test and un-stratified Fisher's exact test of the primary endpoint will be performed using PPS.

To deal with potential missing mUFC at Week 12, imputation methods such as multiple imputation will be used as sensitivity analysis. For patients who discontinued the study early, mUFC collected during the follow-up visit at Week 12 will also be used for sensitivity analysis. If mUFC during the follow up visit is missing at Week 12, patient will be considered as non-responder.

10.5 Secondary objectives

10.5.1 Key secondary objective(s)

The key secondary objective is to assess the complete response rate (proportion of enrolled patients with mUFC $\leq$ ULN) in both arms combined at Week 36 in patients receiving osilodrostat treatment.

The statistical null hypothesis states that the proportion of complete response rate at Week 36 is < 30%. The analysis of the key secondary objective will be based on the 2-sided 95% exact confidence interval (CI) constructed using the Clopper-Pearson method in FAS patients receiving osilodrostat treatment. Patients with missing mUFC at Week 36 will be counted as non-responders. If the lower bound of this 95% confidence interval is $\geq$ 30%, the null hypothesis will be rejected and the complete response rate will be considered at least 30% at Week 36. Patients randomized to placebo who do not switch to osilodrostat will not be included in this analysis.

The above testing on the key secondary objective will only be carried out if the null hypothesis for the primary objective is rejected. This sequential procedure will ensure preservation of the overall 2-sided type 1 error at 5%.

As supportive analysis of the key secondary objective, analysis will be repeated using PPS patients receiving osilodrostat treatment. In addition, the same analysis will be performed in the patients randomized to osilodrostat arm only. For each supportive analysis, the 2-sided 95% exact confidence interval of the complete response rate at Week 36 will be provided.

Patients with missing mUFC at Week 36 will be considered as non-responders for key secondary analysis. In order to evaluate the impact of missing mUFC, imputation method such as multiple imputations will be considered as sensitivity analyses.

10.5.2 Other secondary efficacy objectives

10.5.2.1 Assess the overall response rate at Week 12, Week 36, and Week 48

Proportion of overall responders (enrolled patients with mUFC ≤ ULN or have at least 50% reduction in mUFC from baseline and > ULN) at Week 12, Week 36 and Week 48 will be summarized using point estimates and Clopper-Pearson 95% Cis by treatment arms and for overall patients. For the osilodrostat arm, denominator will be the number of patient randomized to osilodrostat; whereas for placebo arm, denominator will be number of randomized patients switched to osilodrostat.

10.5.2.2 Assess the change in mUFC during the Core and optional Extension periods of the study

For the actual and percentage change in mUFC from baseline, descriptive summaries will be provided for every visit in Core and optional extension phase at which UFC is collected. 95% CIs for the percentage change from baseline will also be provided by treatment arms and for overall patients.

10.5.2.3 Compare the time-to-first control of mUFC during the placebo-controlled period between patients randomized to osilodrostat and placebo

Time-to-first control of mUFC during the placebo control period will be analyzed using Kaplan-Meier plots and the logrank test. Time-to-first control of mUFC is defined as the time (in days) from randomization to the time of the first post-baseline mUFC collection that was ≤ ULN (based on central lab result) before discontinuation or completion of placebo-controlled period, whichever is earlier.

10.5.2.4 Assess the time-to-escape during treatment of osilodrostat up to Week 48

For patients who attained normal mUFC (≤ ULN), time-to-escape will be analyzed using Kaplan-Meier plots. This will be performed by randomized treatment assignment and for the overall trial population. Time-to-escape is defined as the time (in weeks) from the first collection of post-baseline normal mUFC (≤ ULN) to the first mUFC > 1.3 x ULN on 2 consecutive visits on the highest tolerated dose of osilodrostat and not related to a dose interruption or dose reduction due to safety reasons. Time-to-escape will not be assessed for patients during the first 26 weeks.

Patients that have dose interruption or dose reduction for safety reasons will be censored at the time of the first dose interruption.

10.5.2.5 Assess the change from baseline in cardiovascular and metabolic related parameters associated with Cushing's disease during the core period of the study

For cardiovascular and metabolic parameters associated with Cushing's disease (e.g. fasting glucose, HbA1c, fasting lipid profile, SBP, DBP, weight and waist circumference):

For actual and percentage change from baseline to Week 12, Week 36 and Week 48, descriptive summaries will be provided by treatment arm and for overall patients.

For the actual and percentage change from the baseline to the end or the last available measurement of the placebo control period, whichever occurs earlier, in addition to the descriptive summary, the mean difference between two randomized arm and associated 2-sided 95% C.I. will be estimated with adjustment for corresponding baseline parameter value. In addition, shift tables using normal/abnormal categories for BP (SBP, DBP), FPG, HbA1c, fasting lipid profile, weight and waist circumference from baseline at Week 12, 36, and 48 by randomized arms and for overall patients will be assessed. Normal for these parameters is defined as shown in Appendix 3.

10.5.2.6 Assess the change from baseline in physical features of Cushing's disease

For each of physical features of Cushing's disease: facial rubor, hirsutism (female only), striae, supraclavicular fat pad, dorsal fat pad, proximal muscle wasting (atrophy), central (abdominal) obesity, and ecchymoses (bruises), Likert scores will be measured. The change from baseline at Weeks 12, 36 and 48 will be assessed using by randomized treatment arm and for overall patients.

10.5.2.7 Assess the change from baseline in bone mineral density by DXA scan at Week 48

For bone mineral density measured by DXA scan at the lumbar spine and total hip, descriptive summaries of actual and percentage change from baseline at Week 48 will be provided by randomized treatment arm and for overall patients.

10.5.2.8 Assess the change from baseline in serum, salivary and hair cortisol levels

Change in the actual and percentage change from baseline to each post-baseline visit for serum cortisol, late night salivary cortisol, morning salivary cortisol and hair cortisol levels will be assessed. Descriptive summaries will be provided for every visit in the Core and Extension phases at which the biomarkers of hypercortisolism are collected. Salivary cortisol samples will only be included if they are collected within the correct time window. 95% CIs for the percentage change from baseline will also be provided by treatment and for overall patients.

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

The assessment of safety will be based mainly on the frequency and severity of AEs and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e.g. ECG, vital signs, and special tests) will also be presented. All safety outputs will use the SS, which consists of all patients that received at least one dose of osilodrostat or placebo. Safety data will be presented in two different periods as defined below.

- Placebo-controlled period: patients randomized to osilodrostat, patients randomized to placebo, and overall patients

- Overall study period: patients randomized to osilodrostat, patients randomized to placebo, and overall patients
- The overall observation period will be divided into three mutually exclusive segments:
- pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
- on-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
- 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) have to include only AEs that started or worsened during the on-treatment period, the ***treatment-emergent*** AEs. However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged.

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

Serious adverse events, non-serious adverse events and adverse events of special interest (AESI) during the on-treatment period will be tabulated.

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

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

10.5.3.3 Laboratory abnormalities

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

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

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

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

- Listing of all laboratory data with values flagged to show the corresponding CTCAE v4.03 grades if applicable and the classifications relative to the laboratory normal ranges

For laboratory tests where grades are defined by CTCAE v4.03

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each patient will be counted only once for the worst grade observed post-baseline.

- Shift tables using CTCAE v4.03 grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE v4.03,

- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value.

10.5.3.4 Other safety data

ECG

ECG data will be summarized with

- shift table baseline to worst on-treatment result for overall assessments
- Number and percentage of patients with clinically notable QT/QTcF interval values will be summarized.
- listing of ECG evaluations for all patients with at least one abnormality.

Vital signs

Vital signs (supine BP, HR & temperature) reporting of results will include

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

Tumor volume and longest dimension

Tumor volume and longest dimension will be evaluated as defined in Section 7.2.2.6

The longest dimension (in mm) will be summarized as absolute values and actual and percent change from baseline in longest dimension. The tumor invasiveness is also evaluated, in terms of the prevalence of tumors with extension outside sella turcica and/or invasion into surrounding structures at baseline and during the study (new onset/disappearance).

In addition, if the tumor volume is evaluated, a descriptive summary of actual tumor volumes as well as actual and percent change from baseline in tumor volumes will be provided.

Columbia Suicide Severity Reporting Scale (C-SSRS)

C-SSRS data will be mapped to Columbia Classification Algorithm for Suicide Assessment (C-CASA) as per FDA guidance on suicidality (Food and Drug Administration 2010). The proportion of patients who have completed suicide, suicide attempt, preparatory actions toward imminent suicidal behavior, suicidal ideation, and self-injurious behavior without suicidal intent will be summarized by treatment arm. The number of patients with SAEs referring to a positive suicidal evaluation will be summarized by treatment arm.

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, and will include arithmetic and geometric mean, median, SD, CV, geometric CV, minimum and maximum. Zero concentrations will not be included in the geometric mean calculation. Graphical depiction (mean and individual) for osilodrostat concentrations and/or profiles (if applicable) during the course of the study will be performed by incident dose and visit. Additional details on PK data analysis will be specified in the statistical analysis plan.

[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 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 CushingQoL score is identified as the primary PRO variable of interest. EQ-5D utility index and visual analogue scale (VAS) scores, and Beck Depression Inventory-II (BDI) total

score are identified as secondary PRO variables of interest. The FAS will be used for analyzing PRO data. No multiplicity adjustment will be applied.

Change from baseline in the CushingQoL score during Study Period 1 and 2 will be analyzed using a linear mixed effect model for longitudinal data to assess the treatment effect over time. The differences in least square means between osilodrostat and placebo arm, and the corresponding 2-sided 95% confidence interval (CI) at each time point will be presented. Descriptive statistics will be used to summarize the raw and absolute change from baseline for the scores at each scheduled assessment including critical time points such as from baseline to Week 12 and Week 48, from Week 12 to Week 36 and from Week 36 to Week 48 etc. during both Core phase (Study Period 1 and 2) and the optional extension phase.

Similar analyses will be performed for EQ-5D utility index and visual analogue scale (VAS) scores, and Beck Depression Inventory-II (BDI) total score.

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. Patients with baseline and at least one non-missing post-baseline assessments during the Core phase will be included in the linear mixed effect model analysis. All available data until completion or early discontinuation during Core phase will be used in the linear mixed effect models analyses with missing scores at any time point are assumed to be missing-at-random (MAR).

[redacted]

10.7 Interim analysis

The study will have no planned interim analysis for efficacy. The DMC will conduct periodic safety data reviews as outlined in Section 8.6.

10.8 Sample size calculation

Eligible patients will be stratified at randomization according to history of pituitary irradiation (yes/no). Based on the LCI699C2201 study, it is assumed that approximately 20% of randomized patients will have a history of pituitary radiation.

With 2:1 randomization ratio, to detect a difference of 45% in complete response rate between 60% in osilodrostat arm and 15% in placebo arm (equivalent odds ratio equals 8.5), a sample size of 42 patients in osilodrostat arm and 21 patients in placebo arm will provide 91% power based on a 1-sided CMH exact test at the 0.025 level. In order to adjust for drop-outs, an additional 10% patients will be enrolled. Thus a total of approximately 69 patients will be enrolled in the study.

10.9 Power for analysis of key secondary variables

The analysis of the key secondary objective will be based on the 2-sided 95% confidence interval constructed using the Clopper-Pearson exact method. If the lower bound of this 95% confidence interval is $\geq$ 30%, the null hypothesis will be rejected and the complete response rate will be considered at least 30% at Week 36 . Both the SOM230G2304 trial of Pasireotide LAR and the SOM230B2305 trial of Pasireotide s.c. were powered to show a response rate

where the lower bound of the 95% confidence interval was ≥15%. Therefore an increase in this lower bound of the 95% confidence interval to a threshold of ≥30% would provide a significant improvement in clinical benefit to this patient arm.

The above testing on the key secondary objective will only be carried out if the null hypothesis for the primary objective is rejected. This sequential procedure will ensure preservation of the overall 2-sided type 1 error at 5%.

Assuming a 60% complete response rate at Week 36, and less than 50% discontinuation rate of patients in placebo arm prior to Week 12. For the 69 patients in the pooled population, there is higher than 98% chance that the lower bound of 2-side 95% exact CI (based on Clopper-Pearson method) of the observed response rate is larger than 30%.

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 eCRFs.

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

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

11.4 Discontinuation of the study

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

11.5 Publication of study protocol and results

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

11.5.1 Communication and Publication of Clinical Trial Results

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

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

Accordingly, ALL AUTHORS MUST HAVE:

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

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

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) 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 (eCRF) 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 eCRFs and all other required reports. Data reported on the eCRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the eCRF must be recorded. Any missing data must be explained. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to eCRFs.

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

Appendix 1: List of drugs to be used with caution with osilodrostat

Table 14-1 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 Esoprazole **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	**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**:	Enflurane Halothane Isoflurane Methoxyflurane Sevoflurane Acetaminophen Chlorzoxazone Ethanol N, N-Dimethylformamide Theophylline

CYP1A2 substrates	CYP2C19 substrates	CYP2D6 substrates	CYP3A4/5 substrates	CYP2E1 substrates
		Tricyclics/ tetracyclics: Desipramine[1] Amitriptyline Clomipramine Doxepin Imipramine Maprotiline Mianserin Mirtazapine 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	Aripiprazole Haloperidol Lurasidone[1] Perospirone[1] Pimozide[2] Quetiapine[1] **Immune Modulators:** Cyclosporine[2] Everolimus[1] Sirolimus[1,2] 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] **Corticosteroids:** Budesonide[1] Fluticasone[1] **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]	

CYP1A2 substrates	CYP2C19 substrates	CYP2D6 substrates	CYP3A4/5 substrates	CYP2E1 substrates
			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.

Appendix 2: Medications with a “Known risk to cause TdP” and with a “Possible risk to cause TdP”

The following e-link provides a list of medications with a “Known risk to cause TdP” and with a “Possible risk to cause TdP”. These medications are prohibited to be used concomitantly with 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”.

Appendix 3: Normal ranges for cardiovascular risk factors

Parameter	Conventional Units	SI Units	Comment
Systolic blood pressure (SBP)	90-139 mmHg	90-139 mmHg	Conventional and SI units are the same
Diastolic blood pressure (DBP)	60-90 mmHg	60-90 mmHg	Conventional and SI units are the same
Fasting plasma glucose (FPG)	70-115 mg/dL 70-125 mg/dL	3.9-6.4 mmol/L 3.9-6.9 mmol/L	Age 13-49 years Age ≥ 50 years
HbA1c	< 6.5 %	< 6.5 %	Percent of total hemoglobin
Total cholesterol	< 170 mg/dL < 200 mg/dL	0.00-4.35 mmol/L 0.00-5.15 mmol/L	Age 3-19 years Age ≥ 20 years
HDL cholesterol	> 34 mg/dL	> 0.89 mmol/L	All adult ages
LDL cholesterol	0-110 mg/dL 0-130 mg/dL	0.00-2.85 mmol/L 0.00-3.35 mmol/L	Age 3-19 years Age ≥ 20 years
Triglycerides	< 200 mg/dL	2.24 mmol/L	All adult ages SI: Age13-64 years SI: Age ≥ 65 years

Source: Chobanian A, et al JNC 7 (2003). FPG, HbA1c : ADA Diabetes Standards 2015 . Lipids: Central Laboratory Reference Ranges as of writing of original version of this protocol (consult Laboratory Manual for most current information).