NOVARTIS

Clinical Development

LCI699/Osilodrostat

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

Statistical Analysis Plan (SAP)

Author:	Trial statistician, [redacted]
Document type:	SAP Documentation
Document status:	Final v1.0 - Amendment 1
Release date:	01-Apr-2019
Number of pages:	35

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
22-Jun-2016	Prior to FPFV	Creation of final version	Creation of first version	All
01-Apr-2019	Prior to DBL & unblinding	Creation of amendment 1	Change from baseline analysis of serum, salivary and hair cortisol added as a trial objective.	1.2 Study objectives and endpoints 2.7.8 Assess the change from baseline in serum, salivary and hair cortisol levels
			Updated description of the extension period to allow for patients remaining beyond week 96	1.1.4 Extnesion phase
			Removal of longidutinal model of change in mUFC for the core and extension period.	2.7.2 Assess the change in mUFC during the Core and Extension periods of the study
			Removal of visit window requirement	2.1.1 General definitions
			Removal of section 2.4.1.3	2.4.1.3 Dose level of osilodrostat
			[redacted] Removal of sections 2.10.1 and 2.10.2, and update of 2.10.3	[redacted]
			Update of PK collection windows	2.2.4 Pharmacokinetic analysis set 2.9 Pharmacokinetic endpoints
			Removal of PRO longitudinal models	2.11 Patient reported outcomes
			Language and grammer updates	Multiple sections

Table of contents

List of abbreviations

ACTH	Adrenocorticotropic Hormone
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AR	Auto regression
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATC	Anatomical Therapeutic Classification
BDI-II	Beck Depression Inventory-II
bid	bis in diem/twice a day
BMI	Body mass index
BMD	Bone mineral density
BP	Blood pressure
CD	Cushing's Disease
CI	Confidence interval
CMH	Cochran-Mentel-Haenszel
CRO	Contract research organization
CSR	Clinical Study report
C-SSRS	Columbia Suicide Severity Reporting Scale
CT	Computed tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DAR	Dose Administration Record
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
DRL	Drug Reference Listing
DXA	Dual-energy X-ray absorptiometry
ECG	Electrocardiogram
FAS	Full Analysis Set
FPG	Fasting plasma glucose
eCRF	Electronic Case Report Form
HbA1c	Hemoglobin A1c
ITT	Intent to treat
IRT	Interactive response technology
LLOQ	The limit of quantitation
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MRI	Magnetic resonance imaging
mUFC	Mean Urine Free Cortisol
NCI	National Cancer Institute
q.d.	Once Daily
PD	Pharmacodynamics
PK	Pharmacokinetics

PAS	Pharmacokinetics analysis set
PD	Protocol deviations
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
PT	Preferred term
qd	Qua'que di'e / once a day
QoL	Quality of Life
QTcF	QT corrected (Fridericia QT formula)
SAE	Serious adverse events
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SOC	System Organ Class
SS	Safety Set
SSD	Study specific document
TBIL	Total bilirubin
TDM	Trial Design Model
TV	Trial Visit
UFC	Urine Free Cortisol
ULN	Upper Limit of Normal
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) describes the planned statistical analysis for the primary clinical study report (CSR) of study LCI699C2302. The analysis will be performed after all patients have completed 48 weeks treatment (the core phase of the study) or discontinued earlier. Data from extension phase will be included in the analysis if prior to data cut-off.

This SAP is formulated according to the information provided in the study protocol. All decisions regarding to the analysis described here, have been made prior to database lock and unblinding of study data.

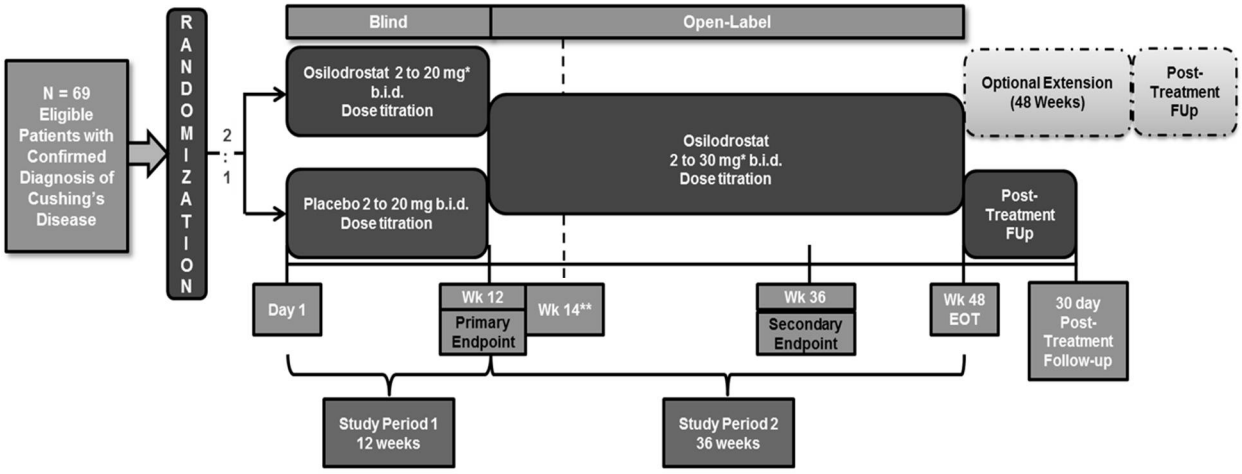
1.1 Study design

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 48 week Extension phase. A schematic diagram of the Core study design is shown below in Figure 1-1. After the screening period, eligible patients are randomized in a 2:1 ratio to osilodrostat or placebo in a 12-week double-blind placebo-control period. At Week12, all patients will enter an open-label osilodrostat treatment period until Week 48, which concludes the core phase of the study. At the end of the core phase, the patients can enter an optional 48-week extension phase.

It is planned to enroll 69 patients in this study, 46 on osilodrostat arm, and 23 in placebo arm. The primary efficacy variable is to assess response rate at Week 12 in the 2 randomized arms. There is no interim analysis planned for this study. The analysis of the primary endpoint will occur after all patients completed the core phase of the study.

A detail description of the study design is presented in the following sections.

Figure 1-1 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

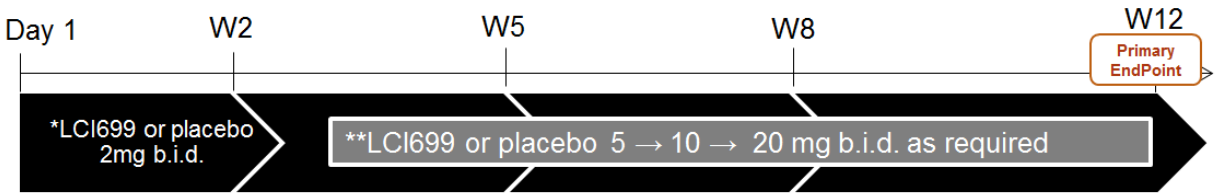
1.1.1 Screening period

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.

1.1.2 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). Study visits occur at Weeks 2, 5, 8, and 12 (Figure 1-2). Study drug is started on Day 1 at a dose of 2 mg b.i.d., and titrated according to the regimen described in protocol Section 6.2, to a dose which lowers mUFC to within the normal range.

Figure 1-2 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.

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 that may disclose the randomized treatment assignment are blinded to patients, investigators and the Novartis Clinical Trial Team. 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.

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, 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.

1.1.3 Period 2 (Weeks 13-48): 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.

During Period 2, the investigator is responsible for dose titration. 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.

1.1.4 Extension phase:

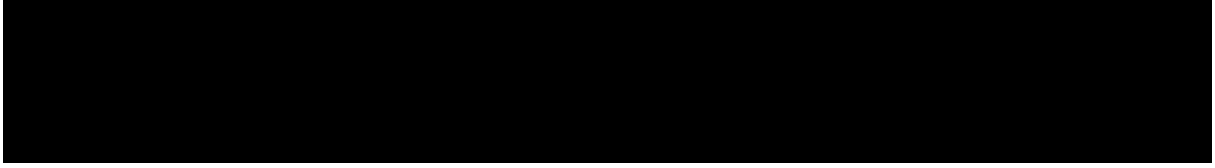
At Week 48, patients have the option to enter a 48 week open-label Extension phase. Patients who do not enter the extension discontinue osilodrostat at Week 48 and conclude with a Post-Treatment (End of Study) visit after 30 days off study drug. Patients who enter the extension phase will continue therapy with osilodrostat for another 48 weeks without interruption. At the end of this extension phase (Week 96), patients will conclude the study with a Post-Treatment (End of Study) visit after 30 days off study drug. 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, 60, 72, and 84. Some patients may remain in the extension phase beyond Week 96, if they are not able to immediately transistion to either the long-term follow up study, or to an alternative treatment.

1.2 Study objectives and endpoints

Table 1-1 Study objectives and endpoints

Objective	Endpoint
Primary	
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	
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	
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) will be provided at Week 12, Week 36, and Week 48 by treatment arm. Response rate will also be provided for all patients in open-label period.
To assess the change in mUFC during the Core and Extension periods of the study.	Actual and percentage change in mUFC from baseline to each post-baseline visit during the Core and Extension at which UFC is collected will be provided by treatment arm. Change will also be provided for all patients in open-label period.

Objective	Endpoint
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.
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 arm and for the overall patient population in the open-label period.
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 for overall population in the open-label period.
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, vital signs, and pituitary MRI, etc..
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, by treatment arms. The change will also be provided for overall population during the open-label period.
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 cortisol markers are collected, by treatment arms and for all patients.



2 Statistical methods

2.1 Data analysis general information

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 at Week 48. The results and outcomes of this analysis will be presented in a CSR. After the Core study phase, patients receiving clinical benefit from osilodrostat treatment have the option to enter a 48-week 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. There is no interim analysis planned for this study.

Novartis or designated CRO will analyze all data using the SAS System for data analysis V9.4 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.

All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

The randomization will be stratified by history of pituitary irradiation. To take stratification into account, the primary efficacy endpoint will be analyzed using Cochran-Mantel-Haenszel (CMH) exact test.

Categorical data or qualitative characteristics of a subject (e.g., gender, race, subject disposition, etc.) will be summarized by frequency count (number of subjects) and percentages. Percentages will be calculated using the number of subjects in the relevant population or subgroup as the denominator.

Continuous data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (mean, standard deviation, median, minimum, and maximum).

2.1.1 General definitions

Study drug

Through out the SAP, investigational drug refers to osilodrostat, and study treatment/ study drug refers to osilodrostat or placebo.

Date of study treatment

The start date of study treatment is defined as the first date when a nonzero dose of study treatment was administered and recorded on DAR eCRF. The date of first administration of study treatment in period 1 will be referred as the start date of study treatment.

The last date of study treatment is defined as the last date when a nonzero dose of study drug was administered and recorded on DAR eCRF.

Study day

Study day is used to represent an evaluation, a measurement or an event (e.g. AE onset, laboratory abnormality occurrence, disease progression, etc). The study day is calculated as

Study day = date of assessment –start date of study treatment + 1 (if date of assessment is after start date of study treatment)

Study day = date of assessment –start date of study treatment (if date of assessment is before start date of study treatment)

For any assessment or events such as baseline characteristics or medical history that is supposed to occur prior to start date of the study treatment, study day will be negative. There is no Day 0 defined.

Study day associated with a UFC assessment

The study day associated with a UFC assessment at any particular visit is defined as the study day of the last UFC sample collection for that visit.

Time unit

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

Baseline

Baseline values for efficacy and safety evaluations are defined as the last assessment available before or on the start date of study treatment. If patients have no assessments as defined above, the baseline result will be missing.

Follow up

Regular safety follow-up is scheduled at 30 days after the last date of study treatment. In addition, for patients who discontinued study treatment during Period 1 (Weeks 1 to 12), reasonable efforts should be made to follow the patients and perform the assessments as indicated in protocol visit evaluation schedule table (protocol Table 7-1a) up to and including Week 12. The data collected during the follow up visits in Period 1 will be used as sensitivity analysis for efficacy, and will be used for safety.

Visit number and time window

The following visit schedule tables are generated from TDM/TV domain.

Table 2-1 Scheduled visits in core phase

Core study Visit	Day/Week	Clarifying Notes
Visit 10	Day -56 to day -1	Screening
Visit 101	Day 1/Week 1	Baseline / Week 1
Visit 102	Day 15/Week 2	Period 1/ Double blind period
Visit 103	Day 36/Week 5	Period 1/ Double blind period
Visit 104	Day 57/Week 8	Period 1/ Double blind period
Visit 105	Day 85/Week 12	Period 1/ Double blind period
Visit 301	Day 15/Week 2 FUP	Period 1/ Double blind period
Visit 302	Day 36/Week 5 FUP	Period 1/ Double blind period
Visit 303	Day 57/Week 8 FUP	Period 1/ Double blind period
Visit 304	Day 85/Week 12 FUP	Period 1/ Double blind period
Visit 106	Day 99/Week 14	Period 2/ Open-label treatment period
Visit 107	Day 120/Week 17	Period 2/ Open-label treatment period
Visit 108	Day 141/Week 20	Period 2/ Open-label treatment period
Visit 109	Day 162/Week 23	Period 2/ Open-label treatment period
Visit 110	Day 183/Week 26	Period 2/ Open-label treatment period
Visit 111	Day 204/Week 29	Period 2/ Open-label treatment period
Visit 112	Day 225/Week 32	Period 2/ Open-label treatment period
Visit 113	Day 253/Week 36	Period 2/ Open-label treatment period
Visit 114	Day 281/Week 40	Period 2/ Open-label treatment period
Visit 115	Day 309/Week 44	Period 2/ Open-label treatment period
Visit 199	Day 337/EOT core	End of treatment core phase
Visit 399	POST TRT FU	Post treatment follow-up
Visit 499	END POST TRT FU	End of post treatment follow-up

Table 2-2 Scheduled visits in extension phase

Extension study Visit	Day/Week	Clarifying Notes
Visit 201	Day 365/Week 52	Extension
Visit 202	Day 393/Week 56	Extension
Visit 203	Day 421/Week 60	Extension
Visit 204	Day 449/Week 64	Extension
Visit 205	Day 477/Week 68	Extension
Visit 206	Day 505/Week 72	Extension
Visit 207	Day 589/Week 84	Extension
Visit 299	Day 673/EOT EXTN	End of treatment extension phase
Visit 399	POST TRT FU	Post treatment follow-up
Visit 499	END POST TRT FU	End of post treatment follow-up

2.2 Analysis sets

2.2.1 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. The randomization is stratified by history of pituitarory irradiation yes/no.

2.2.2 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.

2.2.3 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. The following protocol deviations will lead to exclusion from PPS.

- Informed consent for core phase not documented
- mUFC or ACTH related inclusion criteria not met
- Pituitary source of excess ACTH is not confirmed

- Cushing's disease confirmation is missing
- Pituitary surgery related inclusion criteria not met
- Pituitary irradiation related inclusion criteria not met
- Washout period related inclusion criteria not met
- Participation in another trial with an investigational drug does meet the exclusion criteria
- Subject pregnant or lactating at study entry does mee the exclusion criteria
- Subject's history of inherited syndrome as cause for hormone over secretion does meet the exclusion criteria
- Subject's medical history of Cushing's syndrome due to ectopic ACTH secretion or ACTH-independent (adrenal) Cushing's syndrome does meet the exclusion criteria
- Subject's moderate or severe renal impairment does meet the exclusion criteria
- Subject met the discontinuation criteria, but was not discontinued from the trial *
- Subject took a prohibited concomitant medication **
- *if PD occurs before Week 12, exclude from PPS, if occurs between Week 12 and Week 36, exclude from PPS for key secondary analysis
- **if PD occurs between Week 12 and Week 36, exclude from PPS for key secondary analysis. Not applicable for primary analysis.

2.2.4 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.
A PK concentration is considered as non evaluable if:

- The patient didn't receive the incident dose (last dose administered prior to PK collection) as planned per protocol, or
- If the elapsed time between PK sample and prior dose didn't fall within acceptable window:
    - pre-dose samples within 0.5 h before dose administration, and within 9h to 15h after the previous dose
    - post-dose samples with elapsed time within nominal time range (i.e. within 1h to 2h),
    - 12h PK sample with elapsed time within 9h to 15h after previous dose.
- Or if vomiting occurs within 4 hours after the last intake prior to the PK sample draw.

Additionally, a PK concentration or parameter can be considered non-evaluable as per scientific judgment of the clinical pharmacology expert; reasons will be documented. Such PK concentration and parameter will be excluded from PK [redacted] tables/figures, but will be included in listings with flags and reasons for exclusion.

2.2.5 Withdrawal of informed concent

Any data collected in the clinical database after a subject withdraws informed consent from all further participation in the trial, will not be included in the analysis datasets. The date on which a patient withdraws full consent will be recorded in the eCRF.

Third party data e.g. PK, biomarker etc. collected in the clinical database without having obtained consent for collection will not be included in the analysis datasets. These data will be excluded by the presence of the appropriate protocol deviation criterion.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Demographics and 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.

Demographic variables include Age (in year), Age category ($< 65/\geq 65$), gender, race, and ethnicity.

Baseline disease characteristics include time to first LCI699 dose since diagnosis of Cushing's disease, Cushing's disease status (de novo or persistent/recurrent), use of previous treatment, or surgery, mean UFC at baseline.

2.3.2 Patient disposition

The number of screened patients and number of patients randomized will be tabulated. The summary will be produced for all pre-screened patients. Reasons for screening failure will be summarized and listed.

Patient disposition will be tabulated for FAS. The summary will include the number of patients who were randomized, treated, ongoing, permanently discontinued from study treatment.

The following summaries will be presented: % is based on total number of FAS patients:

- Number (%) of patients who were randomized (based on data from IRT system)
- Number (%) of patients who were randomized but not treated (based on eCRF DAR page not completed for any study treatment component)
    - Primary reason for not being treated (based on eCRF End of Treatment Phase Completion page)
- Number (%) of patients who were treated (based on eCRF DAR page of each study treatment component completed with non-zero dose admistered)
    - Number (%) of patients who are still on treatment (based on eCRF End of Treatment Phase page not completed)

- Number (%) of patients who discontinued the study treatment phase (based on eCRF End of Treatment Phase page)
  - Primary reason for study treatment phase discontinuation (based on eCRF End of Treatment Phase Completion page)
  - Number (%) of patients who entered post-treatment follow up
    - Number (%) of patients who discontinued from post-treatment follow-up
      - Primary reason for discontinuation from post-treatment follow-up
  - Number (%) of patients who discontinued in Period 1(prior to Week 12)
    - Primary reason for discontinuation in Period 1
  - Number (%) of patients who discontinued in Period 2 (Weeks 13 to 48)
    - Primary reason for discontinuation in Period 2
- Number (%) of patients who completed core phase (week 48)
  - Completed Week 48 and did not enter Extension phase
  - Completed Week 48 and entered Extension phase
    - Number (%) of patients who are ongoing in Extension
    - Number (%) of patients who discontinued in the Extension
      - Primary reason for discontinuation in the Extension
    - Number (%) of patients who completed extension

* Patients who completed Week 48 and did not enter extension phase are not counted as discontinuations.

2.3.3 Medical history

Relevant medical history and ongoing medical conditions at baseline will be summarized and listed. The summary will be presented using FAS by primary system organ class (SOC), preferred term (PT), by treatment group and all patients.

2.3.4 Protocol deviations

The number (%) of patients in FAS with any PDs wil be tabulated by deviation category (as specified in the study specification document (SSD) by treatment group. Major PDs leading to exclusion from PPS will be tabulated separately by treatment group. All PDs will be listed.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

2.4.1.1 Duration of exposure

The exposure to the study drug will be summarized based on study periods, i.e., period 1 and period 2, and overall period by treatment group.

Period 1 (Week 1 to Week 12)

Duration of exposure (weeks) = (min (date of Week 12 visit – 1, date of last date of study treatment, date of data cut-off, date of death) – date of first date of study treatment + 1)/7

Period 2 (Week 13 to Week 48)

Duration of exposure (weeks) = (min (date of Week 48 visit, date of last date of study treatment, date of data cut-off, date of death) – date of first date of study treatment in period 2 (Week 12 visit) + 1)/7

Overall Period

Duration of exposure (weeks) = (min (date of last date of study treatment, date of data cut-off, date of death) – date of first date of study treatment + 1)/7

In the overall period, the total duration of exposure to study treatment is considered by taking account of the duration of exposure in both Period 1, Period 2, as well as extension. Patients in osilodrostat arm will have exposure only to osilodrostat, and patients in placebo arm will have exposure to both osilodrostat and placebo presented separately.

The above duration calculation includes the periods of temporary interruptions.

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

2.4.1.2 Dose reduction/interuption

The number of patients who have at least one dose reduction or interruption, and the corresponding reasons will be summarized by study period. Although patients may have multiple dose reductions or interruptions with the same reason, patients will be counted only once for each distinct reason.

The total daily dose administered and reason for dose change will be listed with UFC information by date.

2.4.2 Prior, concomitant and post therapies

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) other than the study treatment administered to a patient coinciding with the study treatment period. Concomitant therapy include medications (other than study drugs) starting on or after the start date of study treatment or medications starting prior to the start date of study treatment and continuing after the start date of study treatment.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Reference Listing (DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (ATC) classification system and summarized by lowest ATC class and preferred term using frequency counts and percentages. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and preferred term.

All concomitant therapies will be listed. Any concomitant therapies starting and ending prior to the start of study treatment or starting more than 30 days after the last date of study treatment or safety follow-up whichever is later will be flagged in the listing. The safety set will be used for all concomitant medication tables and listings.

Concomitant medications and significant non-drug therapies will be summarized using frequency counts and percentages by ATC class, preferred term and treatment group within each of three study periods: Period 1 (Week 1 to Week 12), Period 2 (Week 13 to Week 48), and overall study period. If a patient discontinued from study in Period 1, the concomitant medications taken during the follow-up period will be summarized in Period 1 and overall period.

2.5 Analysis of the 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.

2.5.1 Primary endpoint

The primary efficacy variable is the proportion of randomized patients in each treatment arm who are complete responders at Week 12. A complete responder is defined as a patient who has mUFC ≤ ULN (based on central lab result) at Week 12. Patients who discontinued the study during the placebo-control period will be counted as non-responders for the primary endpoint. Dose reductions and temporary dose interuptions for safety reason during the placebo-control period do not preclude patients from being counted as a complete responder for the primary endpoint.

2.5.2 Statistical hypothesis, model, and method of analysis

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

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.

2.5.3 Handling of missing values/censoring/discontinuations

It is scheduled to collect three individual 24 hours Urine Free Cortisol (UFC) samples at visits Week 1, 12, 36, and 48, and two UFC samples at all other visits. For a given visit, Mean Urine

Free Cortisol (mUFC) is the mean of all available (with a minimum of 2) individual UFC values determined at a central laboratory. In the case that only one or no 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 protocol visit evaluation schedule table (Table 7-1a). 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.

2.5.4 Supportive 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, , multiple imputation assuming missing at random will be performed as a 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, the patient will be considered as a non-responder.

2.6 Analysis of the key secondary objective

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.

2.6.1 Key secondary endpoint

The key secondary efficacy variable is the proportion of complete responders at Week 36 in FAS patients receiving osilodrostat treatment. A complete responder is defined as an enrolled patient who has mUFC $\leq$ ULN at Week 36. Dose reductions and temporary dose interruptions for safety reasons do not preclude patients from being counted as a complete responder for the key secondary endpoint.

2.6.2 Statistical hypothesis, model, and method of analysis

For the key secondary endpoint, 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.

2.6.3 Handling of missing values/censoring/discontinuations

Placebo patients who discontinued during Period 1 and not received osiltrostat treatment in this study will not be included in the analysis. Patients who received osilodrstat treatment 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, multiple imputations assuming missing at random will be considered as sensitivity analyses.

2.7 Analysis of secondary efficacy objectives

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

Proportion of complete responders (enrolled patients with mUFC ≤ ULN), partial responders (enrolled patients with mUFC > ULN and at least 50% reduction from baseline), and overall responders (enrolled patients with mUFC ≤ ULN or have at least 50% reduction in mUFC from baseline and > ULN) will be summarized using point estimates for every scheduled visit in the core and extension phase at which UFC is collected by treatment arm. Response rate will also be provided for all patients in the open-label period. 95% 2-sided CIs will be provided at Week 12, Week 36 and Week 48. To calculate the response rate during the open label treatment period, for the osilodrostat arm, the denominator will be the number of patients randomized to osilodrostat in Period 1; whereas for the placebo arm, the denominator will be the number of patients randomized to placebo in Period 1 who switched to osilodrostat. The FAS will be used for this analysis.

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

- Change in mUFC from baseline during the placebo-control period only

2.7.3 For the actual value and change in mUFC from baseline during placebo-control period, descriptive summaries will be provided. 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 is defined as the time (in days) from first study treatment date 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. It will be defined as censored at the last mUFC collection date if the mUFC was not controlled during the placebo-controlled period.

Time-to-first control of mUFC during the placebo control period will be analyzed using Kaplan-Meier plots and the logrank test. The quantiles of time-to-first control and corresponding two-sided 95% CI will be calculated using Kaplan-Meier methodology. FAS will be used for this analysis.

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

Escape is defined as the first loss of control of UFC that meets all of the following criteria:

- prior normalization of UFC has occurred (mUFC≤ ULN)
- patient reached highest tolerated dose of osilodrostat
- 2 consecutive mUFC (collected at scheduled visits) were above 1.3x ULN
- the loss of control of UFC is not related to a dose interruption or dose reduction due to safety reasons
- happens beyond Week 26 when the patients have a chance to be treated with doses as high as 30 mg bid

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 scheduled visits on the highest tolerated dose of osilodrostat and not related to a dose interruption or dose reduction due to safety reasons after Week 26.

The highest tolerated dose is defined as

- 30 mg bid if reached, or
- being on a reduced dose due to safety reasonse such as AEs, or
- being on the same dose for at least 3 scheduled visits if the previous two criteria are not met.

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 using FAS. The quartiles of time to escape and corresponding two-sided 95% confidence interval will be calculated using Kaplan-Meier methodology. In addition, time-to-escape will be summarized using descriptive statistics for patients who escape. 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. Patients who discontinued the study are considered as censored. Patients who were controlled until the end of the study will be censored at the last mUFC collection date. FAS will be used for this analysis.

2.7.5 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 value and change from baseline to Week 12, Week 36 and Week 48, descriptive summaries will be provided by treatment arm and for overall patients in open-label period.

For the actual value and change from the baseline to Week 12 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 arms 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 to Week 12, 36, and 48 by randomized arms and for overall patients during the open-label period will be assessed. Normal for these parameters is shown in protocol Appendix 4. FAS will be used for this analysis.

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

For each of physical features of Cushing's disease: facial rubor, 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 by shift tables in each of the randomized treatment arms. The change will also be provided for overall patients in open-label period. In addition, the proportions of patients having a favourable shift from baseline to post-baseline time points will be tabulated. FAS will be used for this analysis.

2.7.7 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 to Week 48 will be provided by randomized treatment arm and for overall patients. FAS will be used for this analysis.

2.7.8 Assess the change from baseline in serum, salivary andor hair cortisol levels

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 cortisol markers 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 arms and for all patients.

2.8 Safety 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 who received at least one dose of osilodrostat or placebo. Safety data will be presented by two different periods in different treatment groups as descrbied below.

- Placebo-control period: osilodrstat arm, placebo arm

- Overall study period: osilodrstat arm, placebo arm excluding placebo-control period, and overall patients (excluding safety data of placebo arm collected during placebo-control period)

    * Safety summarized during overall study period focuses on safety of osilodrostat treatment, safety of placebo arm is summarized during placebo-control period.

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 31 days after last dose of study medication.

2.8.1 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 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.

AEs will be summarized by number and percentage of subjects having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A subject with multiple occurrences of an AE will be counted only once in the respective AE category. A subject with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event.

In AE summaries the primary system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their frequency in the osilodrostat arm.

The following adverse event summaries will be produced by treatment; overview of adverse events and deaths (number and % of subjects who died, with any AE, any SAE, any drug reductions/interuptions), AEs by SOC and PT, summarized by relationship (all AEs and AEs related to study treatment), seriousness (SAEs and non-SAEs), leading to treatment discontinuation, leading to dose interruption/adjustment, requiring additional therapy and leading to fatal outcome. In addition, for the summary of serious and non-serious adverse events the number of occurrences will be produced (an occurrence is defined as >1 day between start and prior end date of record of same preferred term).

2.8.1.1 Adverse events of special interest / grouping of AEs

Groupings of AEs of special interest consist of adverse events for which there is a specific clinical interest in connection with osilodrostat treatment (i.e. where osilodrostat may influence a common mechanism of action responsible for triggering them) or adverse events which are similar in nature (although not identical).

An Excel file with the exact composition of the adverse events groupings is available in the CREDI folder "/CREDI Projects/L/LCI699C/Administrative files/CIS (Clinical Information Sciences)/Biostatistics" which is to be used to map reported adverse events to the adverse events groupings. This file is updated periodically after MedDRA update and/or review of accumulating trial data. Prior to database lock, the file will be copied to proper CREDI study specific folder such as RAP folder.

2.8.2 Deaths

All deaths (on-treatment and post-treatment) will be produced by treatment arm, system organ class and preferred term. Post treatment deaths will be flagged

2.8.3 Laboratory data

Laboratory data summaries will include all assessments available for the lab parameter collected no later than 30 days or safety follow-up whichever is laterafter the last study treatment admistration date using data from all sources. All laboratory assessments will be listed and those collected later than 30 days after the last study treatment date will be flagged in the listings.

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 that are graded for both low and high values, summaries will be done separately and labeled by direction, e.g., sodium will be summarizedas hyponatremia and hypernatremia.

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

For laboratory tests where grades are defined by CTCAE

- Summary table for AEs of grades 3 or 4
- 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 grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE ,

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

In addition, the following laboratory results will be summarized.

- Selected laboratory data will also be displayed by presenting summary statistics of change from baseline value
- Patients meeting categorical liver function test criteria, including Hy's Law criteria for liver injury (ALT or AST > 3 x ULN and TBIL ≥ 2 x ULN and ALP < 2 x ULN), e-dish plot may be provided as well

The following listings will be produced for the laboratory data:

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

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

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.

The notable criteria for PR are

- > 200 ms post-baseline and ≤ 200 ms at baseline
- Increase > 25% compared to baseline to a post-baseline value > 200 ms

The notable criteria for QRS are

- > 110 ms post-baseline and ≤ 110 ms at baseline
- Increase > 25% compared to baseline to a post-baseline value > 110 ms

The notable criteria for QT and QTcF are

- > 450 ms at any post-baseline and ≤ 450 ms at baseline
- > 480 ms at any post-baseline and ≤ 480 ms at baseline
- > 500 ms at any post-baseline and ≤ 500 ms at baseline
- an increase from baseline > 30 ms at any post-baseline
- an increase from baseline > 60 ms at any post-baseline

2.8.4.2 Vital signs

All vital signs data (height (cm), weight (kg), body temperature (^{0}C), supine pulse rate (beats per minute), and supine systolic/diastolic blood pressure (mmHg)) will be listed by patient and visit/time, and abnormalities will be flagged on listing. For blood pressure, two measuments are planned to be taken and the average will be used for analysis purpose. Shift table based on notable value will be provided for vital signs. Change over time from baseline will be summarized.

The criteria for clinically notable abnormalities are defined as follows:

Clinically notable elevated values

- Systolic BP: ≥ 180 mmHg and an increase ≥ 20 mmHg from baseline
- Diastolic BP: ≥ 105 mmHg and an increase ≥ 15 mmHg from baseline.
- Supine pulse: ≥ 120 bpm with increase from baseline ≥15 bpm
- Weight: Increase from baseline of ≥ 10%

Clinically notable below normal values

- Systolic BP: ≤ 90 mmHg and a decrease ≥ 20 mmHg from baseline
- Diastolic BP: ≤ 50 mmHg and a decrease ≥ 15 mmHg from baseline
- Supine pulse: ≤ 50 bpm with decrease from baseline ≥ 15 bpm
- Weight: Decrease from baseline of ≥ 5%

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.

2.8.4.3 Tumor volume and longest dimension

For tumor volume evaluated by MRI (or CT) scanning, descriptive summary of actual tumor volumes as well as its change from baseline will be provided at visits where evaluation is scheduled (Week 26, 48, 72, and 96). For MRI (or CT) images that are not interpretable for tumor volume, the longest dimension (in mm) will be summarized instead. Due to evaluation schedule, this analysis will only be performed for the overall study period.

2.8.4.4 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 committed suicide, attempted suicide, done 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.

2.9 Pharmacokinetic endpoints

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.

Listing of all PK parameters will be provided by patient and visit:

- Ctrough as defined by pre-dose concentration collected within 0.5h prior to dosing and within 9h to 15h after the previous dose and
- and Cmax, defined as concentration collection within 1-2hr post-dose.

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.

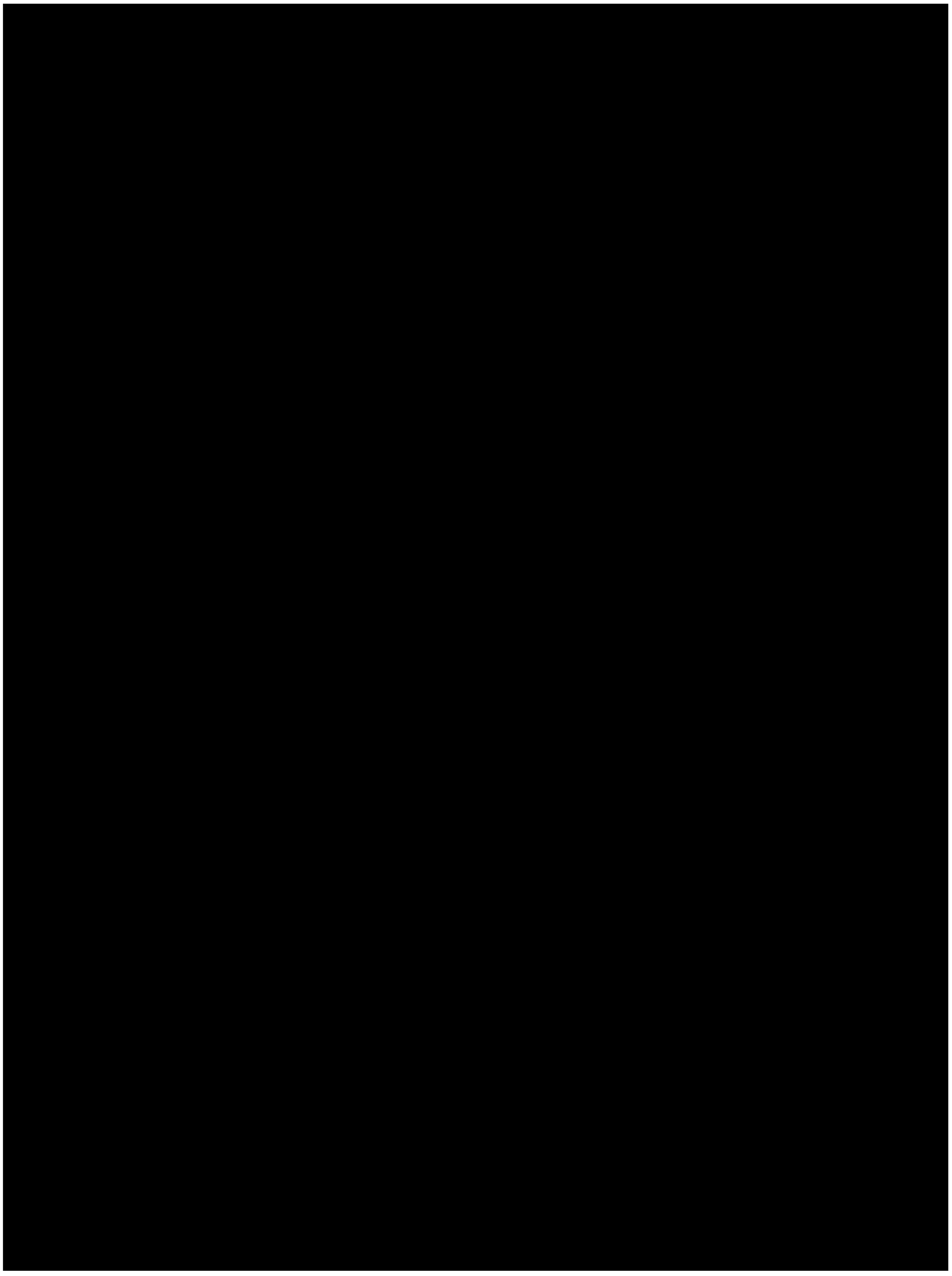
[redacted]

2.11 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.

Descriptive statistics will be used to summarize the actual and 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.

[redacted]



[redacted]

2.14 Interim analysis

The study will have no planned interim analysis for efficacy. The DMC will conduct periodic safety data reviews and dosing review as outlined in DMC charter.

3 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.

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 ≥ 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%.

4 Change to protocol specified analyses

In the SAP, clarification is made that efficacy will be summarized by randomized treatment arms during the placebo-control period. The same analysis will be performed by randomized treatment arms and for overall patients during the open-label period.

Safety will be summarized by randomized treatment arms during the placebo-control period. For the overall study period, only safety data associated with osilodrostat treatment will be summarized, which means safety data in placebo-arm collected during placebo-control period will be excluded from the analysis.

5 Appendix

5.1 Imputation rules

Parital dates will remain partial in the data listings. For the purpose of analysis, the following imputation rules will be used to impute the partial dates.

5.1.1 Study drug

Any partial dates or gaps between dates should be resolved for analysis purpose. The end date of study drug is derived by using the last non-zero dose end date from the dose administration record CRF page. If after DBL the partial dates still exist for end date, the imputation rule is as below:

If month and year is present, but day is missing, set the end date to be the first day of the month. If after imputation of day, study medication end date is earlier then study medication start date set study medication end date to study medication start date.

5.1.2 AE date imputation

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 post-treatment period) will be listed and those collected during the pre-treatment and after 30 days of post- treatment period or safety follow-up whichever is later are to be flagged.

Any missing onset date, causality, or severity must be queried for resolution. Unsolved missing values will be imputed according to the following:

AE end date imputation:

1. If the AE end date month is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, 31DECYYYY, date of death).
2. If the AE end date day is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, last day of the month, date of death).
3. If AE year is missing or AE is ongoing, the end date will not be imputed.

AE start date imputation:

1. If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
2. If the AE start date year value is less than the treatment start date year value, the AE started before treatment. Therefore:

a. If AE month is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).

b. Else if AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).

3. If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore:

   a. If the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).

   b. Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

4. If the AE start date year value is equal to the treatment start date year value:

   a. And the AE month is missing the imputed AE start date is set to the AE reference start date + 1 day.

   b. Else if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).

   c. Else if the AE month is equal to the treatment start date month or greater than the treatment start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date.

5.1.3 Concomitant medication date imputation

The start/stop dates recorded in the electronic case report form (eCRF) will be used to identify when a concomitant medication or a significant non-drug therapy was taken during the study. Concomitant medications and significant non-drug therapies after the start of the study treatment will be listed and summarized by ATC class and standardized medication term for the Safety Set. These summaries will include medications starting on or after the start of study treatment or medications starting prior to the start of study treatment and continuing after the start of study treatment. Any prior medications and significant non-drug therapies starting and ending prior to the start of study treatment will be listed. These analyses will be based on Safety Set.

Any missing date will be queried for resolution. For any unsolved missing dates, the following rules in the following order will be applied to decide if a concomitant medication or a significant non-drug therapy was taken after the start of the study treatment and to decide if the data should be included in the summary table. Originally collected date will be listed in listings.

CM end date imputation:

1. If CM end day is missing and CM month/year are non-missing then impute CM day as the minimum of treatment end date and the last day of the month.

2. If CM end day/month are missing and CM year is non-missing then impute CM day as the minimum of treatment end date and the end of the year (31DECYYYY).

3. If CM day/month/year is missing then use the treatment end date + 1 day as the imputed CM end date.
4. If imputed CM end date is less than the CM start date, use the CM start date as the imputed CM end date.

1. CM start date imputation:If the CM start date year value is missing, the imputed CM start date is set to one day prior to treatment start date.
2. If the CM start date year value is less than the treatment start date year value, the CM started before treatment. Therefore:
    a. If the CM month is missing, the imputed CM start date is set to the mid-year point (01JulYYYY).
    b. Else if the CM month is not missing, the imputed CM start date is set to the mid-month point (15MONYYYY).
3. If the CM start date year value is greater than the treatment start date year value, the CM started after treatment. Therefore:
    a. If the CM month is missing, the imputed CM start date is set to the year start point (01JanYYYY).
    b. Else if the CM month is not missing, the imputed CM start date is set to the month start point (01MONYYYY).
4. If the CM start date year value is equal to the treatment start date year value:
    a. And the CM month is missing or the CM month is equal to the treatment start date month, then the imputed CM start date is set to one day prior treatment start date.
    b. Else if the CM month is less than the treatment start date month, the imputed CM start date is set to the mid-month point (15MONYYYY).
    c. Else if the CM month is greater than the treatment start date month, the imputed CM start date is set to the month start point (01MONYYYY).

If complete (imputed) CM end date is available and the imputed CM start date is greater than the (imputed) CM end date, then imputed CM start date should be set to the (imputed) CM end date.

5.1.3.1 Prior events date imputation

Partial date of prior events (other than AE and CM) date imputation rules are as below:
If only day is missing then impute to be 15th of month. If both day and month are missing, then impute to June 30th. If entire date is missing then leave as missing. If after imputation, the date is after the first dosing date, then use the first dosing date.

5.1.3.2 Post events and therapies date imputation

Partial date of post events/therapies (other than AE and CM) date imputation rules are as below:
Start date:

- If Day is missing, then impute to the max (reference start date, first day of the month).

- Day and month are missing then impute to the max(reference start date, Jan 1)
- Reference start date will be last date of study treatment administration + 1.

End date: No imputation

5.2 AEs coding/grading

Adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. AEs are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1). The CTCAE grade of 5 (death) is not used; rather, 'fatal' is collected as AE outcome and death information is also collected on a separate eCRF page.

5.3 Laboratory parameters derivations

All laboratory values except FPG and HbA1c, will be converted into SI units and the severity grade calculated using appropriate common toxicity criteria (CTC).

As CTC only grades lab values as grade 1-4, grade 0 will be used when lab value is normal. A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

If sites report WBC differential counts in percentage (%) with corresponding lab normal ranges in terms of %, the % differentials will be converted to absolute differentials as Absolute value = [Value (%)/100] x WBC.

6 Reference

American Diabetes Association, (2010), 'Diagnosis and Classification of Diabetes Mellitus', Diabetes Care, 33, Supplement 1, S62-S69.

Norman GR, Sloan JA, Wyrwich KW (2003) Interpretation of changes in health-related quality-of-life: the remarkable universality of half a standard deviation. Med Care; 41:582-92.

Smith B, Vandenhende F, DeSante K, et al (2000), 'Confidence interval criteria for assessment of dose proportionality', Pharmaceutical research, 17, No 10

NOVARTIS

Clinical Development

LCI699/osilodrostat

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

Statistical Analysis Plan (SAP)

Document type:	SAP Documentation
Document status:	Final
Release date:	01-Dec-2020
Number of pages:	34

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
01-Dec-2020	Prior to Final DBL	Creation of SAP for final analysis	N/A – First version	

Table of contents

List of abbreviations

ACTH	Adrenocorticotropic Hormone
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AR	Auto regression
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATC	Anatomical Therapeutic Classification
BDI-II	Beck Depression Inventory-II
bid	bis in diem/twice a day
BMI	Body mass index
BMD	Bone mineral density
BP	Blood pressure
CD	Cushing's Disease
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CRO	Contract research organization
CSR	Clinical Study report
C-SSRS	Columbia Suicide Severity Reporting Scale
CT	Computed tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DAR	Dose Administration Record
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
DRL	Drug Reference Listing
DXA	Dual-energy X-ray absorptiometry
ECG	Electrocardiogram
FAS	Full Analysis Set
FPG	Fasting plasma glucose
eCRF	Electronic Case Report Form
HbA1c	Hemoglobin A1c
ITT	Intent to treat
IRT	Interactive response technology
LLOQ	The limit of quantitation
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MRI	Magnetic resonance imaging
mUFC	Mean Urine Free Cortisol
NCI	National Cancer Institute
q.d.	Once Daily
PD	Pharmacodynamics
PK	Pharmacokinetics

PAS	Pharmacokinetics analysis set
PD	Protocol deviations
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
PT	Preferred term
qd	Qua'que di'e / once a day
QoL	Quality of Life
QTcF	QT corrected (Fridericia QT formula)
SAE	Serious adverse events
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SOC	System Organ Class
SS	Safety Set
SSD	Study specific document
TBIL	Total bilirubin
TDM	Trial Design Model
TV	Trial Visit
UFC	Urine Free Cortisol
ULN	Upper Limit of Normal
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) describes the planned statistical analysis for the final clinical study report (CSR) of study LCI699C2302. It incorporates analysis of the long-term safety and efficacy of the study, including data collected during both the core phase (up to Week 48) and the optional extension period.

The analysis will be performed after all patients have completed the extension period or discontinued earlier. The analysis of the core phase, including the results of the primary and key secondary outcomes was detailed in the Week 48 CSR written following the DBL which occurred once all patients had completed the core phase or discontinued earlier. Details of these analyses can be found in the corresponding SAP, with cover date 01-Apr-2019.

The content of this SAP is based on the LCI699C2302 protocol v02 released on 20-Dec- 2019.

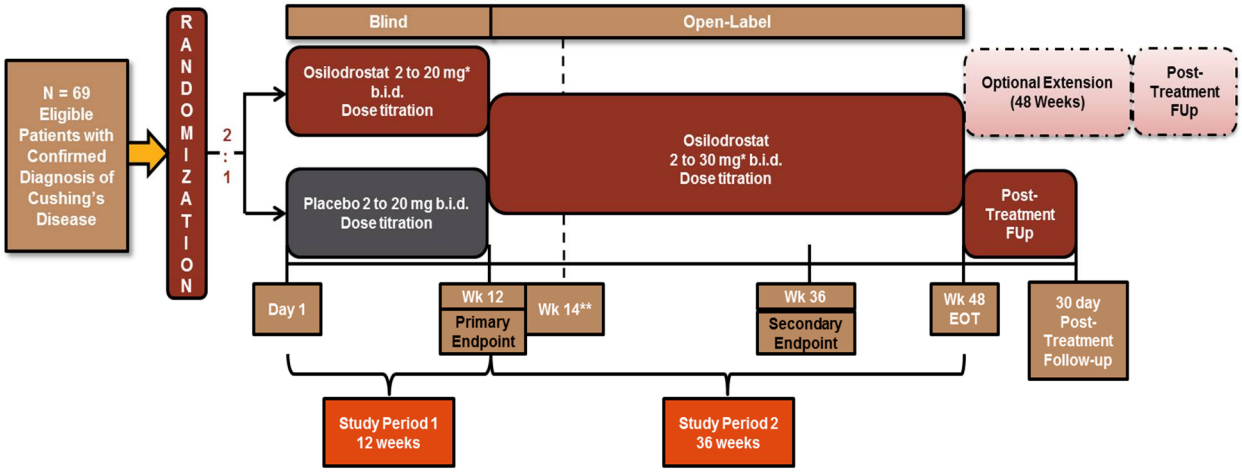
1.1 Study design

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 48-week Extension phase. A schematic diagram of the Core study design is shown below in Figure 1-1. After the screening period, eligible patients were randomized in a 2:1 ratio to osilodrostat or placebo in a 12-week double-blind placebo-controlled period. At Week12, the patients entered an open-label osilodrostat treatment period until Week 48, which concludes the core phase of the study. At the end of the core phase, the patients had the option to enter a 48-week extension phase.

It was planned to enroll 69 patients in this study, 46 on osilodrostat arm, and 23 in placebo arm. The primary objective is to demonstrate the superiority of osilodrostat compared to placebo in achieving a complete response (mUFC $\leq$ ULN) at Week 12. There was no interim analysis planned for this study. The analysis of the primary endpoint occurred after all patients completed the core phase of the study.

A detailed description of the study design is presented in the following sections.

Figure 1-1 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

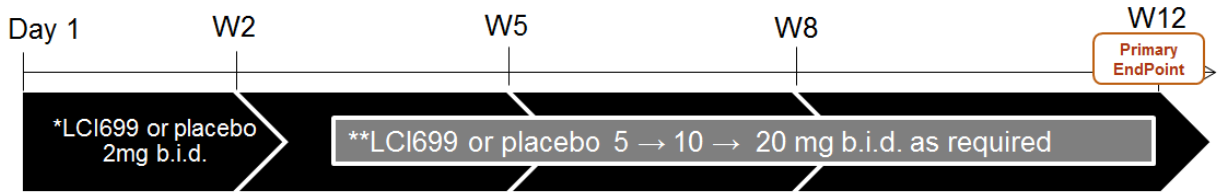
1.1.1 Screening period

The screening period enabled patients to washout their current treatment for Cushing's disease. Patients were evaluated for trial eligibility after the washout period was completed.

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

This is the randomized, double-blind, placebo-controlled period (Weeks 1-12). Eligible patients were 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). Study visits occur at Weeks 2, 5, 8, and 12 (Figure 1-2). Study drug started on Day 1 at a dose of 2 mg b.i.d., and titrated according to the regimen described in protocol Section 6.2, to a dose which lowers mUFC to within the normal range.

Figure 1-2 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.

Three urine samples drawn at 24-hour intervals were collected by patients at screening, within 7 days prior to Day 1 and immediately prior to Week 12 visit (primary endpoint). Two 24-hour urine samples were collected immediately prior to each of the other visits (i.e. at Weeks 2, 5, and 8). The dose was increased if mUFC was above normal (>ULN). The dose was reduced if mUFC <LLN, or if the patient was symptomatic and mUFC was in the lower part of the normal

range. The dose was maintained if mUFC was within the normal range and the patient had no signs or symptoms of adrenal insufficiency.

In order to maintain the treatment blind during Period 1, all laboratory results that may disclose the randomized treatment assignment were blinded to patients, investigators and the Novartis Clinical Trial Team. A group of independent endocrinologists (IEs) was responsible for managing dose titrations during Period 1 between visits. Titrations for patients assigned to placebo aimed to simulate the active arm.

1.1.3 Period 2 (Weeks 12-48, open-label period)

Period 2 started immediately after the Week 12 visit, when the trial became open-label with all patients receiving the active drug, osilodrostat. During Period 2 patients randomized to placebo switched to osilodrostat and underwent their first dose titration with active drug, while patients randomized to osilodrostat continued this treatment and underwent another dose titration.

During Period 2, the investigator was responsible for dose titration. Osilodrostat was titrated up to a maximum dose of 30 mg b.i.d. during this period. Dose titration decisions were made by the investigator based on mean urinary free cortisol (mUFC) results and other relevant patient data.

Three 24-hour urine samples were collected by patients immediately prior to the Week 36 visit (key secondary endpoint) and Week 48 (end of Core phase), two 24-hour samples were collected prior to all other visits in Period 2. A patient was considered to have reached a stable efficacious dose when mUFC remains ≤ ULN. This dose was continued, unless a change was needed.

1.1.4 Optional Extension phase

At Week 48, patients had the option to enter an open-label Extension phase. Patients who did not enter the optional extension discontinued osilodrostat at Week 48 and concluded with a Post-Treatment (End of Study) visit after 30 days off study drug. Prior to Protocol Amendment 02, the optional extension ended at Week 96 for all patients, and patients still deriving benefit from osilodrostat treatment had the option to continue treatment on study until other treatment options became available. After Protocol Amendment 02, patients enrolled in the optional extension phase had to end study participation within 4 weeks after Protocol Amendment 02 was approved at their site, or by Week 96, whichever occurred 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.

During the extension phase the dose of osilodrostat is maintained at the established effective dose unless a change is required based on mUFC results collected at Weeks 48, 60, 72, and 84.

1.2 Study objectives and endpoints

The following table displays the study objectives/endpoints. For the final CSR, not all study objectives will be reported. This is documented in the corresponding SAP section for each objective.

Table 1-1 Study objectives and endpoints

Objective	Endpoint
Primary	
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	
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	
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 optional Extension periods of the study.	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.
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.

Objective	Endpoint
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.

[redacted]

2 Statistical methods

2.1 Data analysis general information

The primary analysis was performed when all enrolled patients 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 at Week 48. The results and outcomes of this analysis were presented in an interim CSR. Analysis for the final CSR will be performed once all patients have either completed the extension period or discontinued earlier.

Novartis will analyze all data using the SAS System for data analysis V9.4 or higher.

The data from all centers participating in the trial will be combined, so that an adequate number of patients will be available for analysis.

2.1.1 General definitions

Study drug

Throughout the SAP, investigational drug refers to osilodrostat, and study treatment/ study drug refers to osilodrostat or placebo.

Overall study period

The overall study period refers to the complete study duration (including core and extension period) with data presented by the osilodrostat arm, placebo arm excluding placebo-control period, and overall patients (excluding data of placebo arm collected during placebo-control period).

Date of study treatment

The start date of study treatment is defined as the first date when a nonzero dose of study treatment was administered and recorded on DAR eCRF. The date of first administration of study treatment in period 1 will be referred as the start date of study treatment.

The last date of study treatment is defined as the last date when a nonzero dose of study drug was administered and recorded on DAR eCRF.

Study day

Study day is used to represent an evaluation, a measurement or an event (e.g. AE onset, laboratory abnormality occurrence, disease progression, etc.). The study day is calculated as

Study day = date of assessment –start date of study treatment + 1 (if date of assessment is after start date of study treatment)

Study day = date of assessment –start date of study treatment (if date of assessment is before start date of study treatment)

For any assessment or events such as baseline characteristics or medical history that is supposed to occur prior to start date of the study treatment, study day will be negative. There is no Day 0 defined.

Study day associated with a UFC assessment

The study day associated with a UFC assessment at any particular visit is defined as the study day of the last UFC sample collection for that visit.

Calculating mean UFC

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

Calculation of proportions of responders

All randomized patients will be included in the analysis for calculating the proportion of responders at time points up to Week 48 based on the FAS.

For calculation of proportion of responders beyond Week 48 (e.g. a time point in extension phase), the following rules will be applied to determine whether patients are included in the analysis.

1) patients who declined to enter optional extension phase after completion of the core phase will be excluded.

2) patients who completed the extension phase will be included until their individual end of study dates (EOT EXT visit, as per Protocol Amendment 02)

3) patients who discontinued prior to the data cutoff date for the Final DBL will be included for visits they could have completed if they had continued until week 96 or data cut off for the analysis (whatever occurs earlier), but excluded for further visits. For example, if the last completed scheduled visit for an early discontinued patient is Week 84, and the time between data cutoff and last completed scheduled visit is 20 weeks, he/she will be included in the analyses up to Week 96.

If included in the analysis for calculating the proportion of responders at a given timepoint, patients who discontinued before this timepoint will be counted as non-responders.

Criteria of adequate follow-up for time points in the extension phase

For a given time point in the extension phase, it will be considered to have adequate follow-up to be included in the reporting activities if there are at least 15 patients available for the analysis at that time point.

Time unit

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

Baseline

Baseline values for efficacy and safety evaluations are defined as the last assessment available before or on the start date of study treatment. If patients have no assessments as defined above, the baseline result will be missing.

Follow up

Regular safety follow-up is scheduled at 30 days after the last date of study treatment. In addition, for patients who discontinued study treatment during Period 1 (Weeks 1 to 12), reasonable efforts should be made to follow the patients and perform the assessments as indicated in protocol visit evaluation schedule table (protocol Table 7-1a) up to and including Week 12.

Visit number and time window

The following visit schedule tables are generated from TDM/TV domain.

Table 2-1 Scheduled visits in core phase

Core study Visit	Day/Week	Clarifying Notes
Visit 10	Day -56 to day -1	Screening
Visit 101	Day 1/Week 1	Baseline / Week 1
Visit 102	Day 15/Week 2	Period 1/ Double blind period
Visit 103	Day 36/Week 5	Period 1/ Double blind period
Visit 104	Day 57/Week 8	Period 1/ Double blind period
Visit 105	Day 85/Week 12	Period 1/ Double blind period
Visit 301	Day 15/Week 2 FUP	Period 1/ Double blind period
Visit 302	Day 36/Week 5 FUP	Period 1/ Double blind period
Visit 303	Day 57/Week 8 FUP	Period 1/ Double blind period
Visit 304	Day 85/Week 12 FUP	Period 1/ Double blind period
Visit 106	Day 99/Week 14	Period 2/ Open-label treatment period
Visit 107	Day 120/Week 17	Period 2/ Open-label treatment period
Visit 108	Day 141/Week 20	Period 2/ Open-label treatment period
Visit 109	Day 162/Week 23	Period 2/ Open-label treatment period
Visit 110	Day 183/Week 26	Period 2/ Open-label treatment period
Visit 111	Day 204/Week 29	Period 2/ Open-label treatment period
Visit 112	Day 225/Week 32	Period 2/ Open-label treatment period
Visit 113	Day 253/Week 36	Period 2/ Open-label treatment period
Visit 114	Day 281/Week 40	Period 2/ Open-label treatment period
Visit 115	Day 309/Week 44	Period 2/ Open-label treatment period
Visit 199	Day 337/EOT core	End of treatment core phase
Visit 399	POST TRT FU	Post treatment follow-up
Visit 499	END POST TRT FU	End of post treatment follow-up

Table 2-2 Scheduled visits in extension phase

Extension study Visit	Day/Week	Clarifying Notes
Visit 201	Day 365/Week 52	Extension
Visit 202	Day 393/Week 56	Extension
Visit 203	Day 421/Week 60	Extension

Extension study Visit	Day/Week	Clarifying Notes
Visit 201	Day 365/Week 52	Extension
Visit 204	Day 449/Week 64	Extension
Visit 205	Day 477/Week 68	Extension
Visit 206	Day 505/Week 72	Extension
Visit 207	Day 589/Week 84	Extension
Visit 299	Day 673/EOT EXTN	End of treatment extension phase
Visit 399	POST TRT FU	Post treatment follow-up
Visit 499	END POST TRT FU	End of post treatment follow-up

2.2 Analysis sets

Analysis sets used for the final CSR are described below. Further analysis sets as defined in the protocol and reported in the core CSR will not be repeated.

2.2.1 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. The randomization is stratified by history of pituitary irradiation yes/no.

2.2.2 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.

2.2.3 Withdrawal of informed consent

Any data collected in the clinical database after a subject withdraws informed consent from all further participation in the trial, will not be included in the analysis datasets. The date on which a patient withdraws full consent will be recorded in the eCRF.

Third party data e.g. PK, biomarker etc. collected in the clinical database without having obtained consent for collection will not be included in the analysis datasets. These data will be excluded by the presence of the appropriate protocol deviation criterion.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Demographics and baseline characteristics

All demographic and baseline disease characteristics were summarized in the interim CSR. They will not be reported in the final CSR.

2.3.2 Patient disposition

Patient disposition will be tabulated for FAS. The summary will include the number of patients who were randomized, treated, permanently discontinued from study treatment.

The following summaries will be presented: % is based on total number of FAS patients:

- Number (%) of patients who were randomized (based on data from IRT system)
- Number (%) of patients who were randomized but not treated (based on eCRF DAR page not completed for any study treatment component)
    - Primary reason for not being treated (based on eCRF End of Treatment Phase Completion page)
- Number (%) of patients who were treated (based on eCRF DAR page of each study treatment completed with non-zero dose administered)
    - Number (%) of patients who discontinued the study treatment phase (based on eCRF End of Treatment Phase page)
        - Primary reason for study treatment phase discontinuation (based on eCRF End of Treatment Phase Completion page)
        - Number (%) of patients who discontinued in Period 1 (prior to Week 12)
            - Primary reason for discontinuation in Period 1
        - Number (%) of patients who discontinued in Period 2 (Weeks 13 to 48)
            - Primary reason for discontinuation in Period 2
- Number (%) of patients who completed core phase (week 48)
    - Completed Week 48 and did not enter Extension phase
    - Completed Week 48 and entered Extension phase
        - Number (%) of patients who discontinued in the Extension
            - Primary reason for discontinuation in the Extension
            - Discontinued at or prior to Week 72 but after Week 48
            - Discontinued prior to Week 96 but after Week 72
            - Discontinued after Week 96
        - Number (%) of patients who completed extension

* Patients who completed Week 48 and did not enter extension phase are not counted as discontinuations.

2.3.3 Medical history

Relevant medical history and ongoing medical conditions were summarized in the interim CSR. They will not be reported in the final CSR.

2.3.4 Protocol deviations

The number (%) of patients in FAS with any PDs will be tabulated by deviation category (as specified in the study specification document (SSD)) by treatment group. All PDs will be listed. In addition, the number (%) of patients in the FAS with any COVID-19 related protocol deviation will be tabulated by deviation category (as specified in the Study Specification Document) overall and by treatment group.

2.3.5 COVID-19 impact

As per Novartis guidance, the start date, in a given country or region, is being defined as the approximate time point at which, according to the WHO situation reports and the Johns Hopkins database, the number of confirmed COVID-19 infections started to increase significantly (around 100 confirmed cases) and/or governments started to take measures (such as stay-at-home orders) to contain the epidemic, whichever occurred first (China: January 1, 2020; Other countries with study sites: March 1, 2020).

The pandemic impact will be assessed based on two subsets:

- Before pandemic set: Patients who completed (or discontinued) the trial before the pandemic start date in their region/country
- During pandemic set: Patients with at least one on-treatment assessment or treatment-emergent event during the pandemic dates as defined for their region/country

A summary of the number of patients in the pandemic sets within each country will be provided. The number of patients who completed or discontinued during the core phase, Week 48-72 and after Week 72 will be tabulated by pandemic set.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

The exposure for study period 1 (week 1-12) and 2 (week 13-48) was summarized in the interim CSR. In the final CSR the exposure to the study drug (osilodrostat) will be summarized for the overall study period including the extension period after week 48.

2.4.1.1 Duration of exposure

Duration of exposure (weeks) = (min (date of last date of study treatment, date of data cut-off, date of death) – date of first date of study treatment + 1)/7

In the overall period, the total duration of exposure to osilodrostat is considered by taking account of the duration of exposure in both Period 1, Period 2, as well as extension. For patients in the placebo arm, exposure to placebo is excluded. The duration calculation includes the periods of temporary interruptions.

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

2.4.1.2 Dose reduction/interruption

The number of patients who have at least one dose reduction or interruption, and the corresponding reasons will be summarized for the overall study period. Although patients may have multiple dose reductions or interruptions with the same reason, patients will be counted only once for each distinct reason.

The total daily dose administered and reason for dose change will be listed with UFC information by date.

2.4.2 Prior, concomitant and post therapies

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) other than the study treatment administered to a patient coinciding with the study treatment period. Concomitant therapy include medications (other than study drugs) starting on or after the start date of study treatment or medications starting prior to the start date of study treatment and continuing after the start date of study treatment.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Reference Listing (DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (ATC) classification system and summarized by lowest ATC class and preferred term using frequency counts and percentages. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and preferred term.

All concomitant therapies will be listed. Any concomitant therapies starting and ending prior to the start of study treatment or starting more than 30 days after the last date of study treatment or safety follow-up whichever is later will be flagged in the listing. The safety set will be used for all concomitant medication tables and listings.

Concomitant medications and significant non-drug therapies will be summarized using frequency counts and percentages by ATC class, preferred term and treatment group within the overall study period.

2.5 Analysis of the primary objective

The primary objective is to demonstrate the superiority of osilodrostat compared to placebo in achieving a complete response (mUFC $\leq$ ULN) at week 12. The results were reported in the interim CSR, and will not be performed for the final analysis.

2.6 Analysis of the key secondary objective

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 results were reported in the interim CSR, and will not be repeated for the final CSR.

2.7 Analysis of secondary efficacy objectives

2.7.1 Assess the overall response rate

Proportion of complete responders (enrolled patients with mUFC ≤ ULN), partial responders (enrolled patients with mUFC > ULN and at least 50% reduction from baseline), and overall responders (enrolled patients with mUFC ≤ ULN or have at least 50% reduction in mUFC from baseline and > ULN) will be summarized using point estimates for all scheduled visits in the core and extension phase at which UFC is collected (provided adequate follow-up, as defined in section 2.1.1, Criteria of adequate follow-up for time points in the extension phase).

Due to the COVID-19 (Coronavirus) pandemic, planned visits may have been cancelled, potentially resulting in missing UFC evaluations. Patients with insufficient information due to any reason at a visit will be considered as non-responder for that visit. The number of patients with non-response due to missing visits linked to the pandemic (recorded as COVID-19 related PD) will be summarized.

To explore the impact of the COVID19 pandemic in the extension phase, individual patient's doses and overall response status over time will be graphically displayed together with pandemic start date.

The FAS will be used for this analysis.

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

For the actual value and change in mUFC from baseline, descriptive summaries will be provided for every scheduled visit in the core and extension (provided adequate follow-up, as defined in section 2.1.1, Criteria of adequate follow-up for time points in the extension phase) at which UFC is collected. The FAS will be used for the analysis.

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

The results were reported in the interim CSR, and will not be repeated for the final CSR.

2.7.4 Assess the time-to-escape during treatment of osilodrostat

Escape is defined as the first loss of control of UFC that meets all of the following criteria:

- prior normalization of UFC has occurred (mUFC≤ ULN)
- patient reached highest tolerated dose of osilodrostat
- 2 consecutive mUFC (collected at scheduled visits) were above 1.3x ULN
- the loss of control of UFC is not related to a dose interruption or dose reduction due to safety reasons

- happens beyond Week 26 when the patients have a chance to be treated with doses as high as 30 mg bid

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 scheduled visits on the highest tolerated dose of osilodrostat and not related to a dose interruption or dose reduction due to safety reasons after Week 26.

The highest tolerated dose is defined as

- 30 mg bid if reached, or
- being on a reduced dose due to safety reasons such as AEs, or
- being on the same dose for at least 3 scheduled visits if the previous two criteria are not met.

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 using FAS. The quartiles of time to escape and corresponding two-sided 95% confidence interval will be calculated using Kaplan-Meier methodology. In addition, time-to-escape will be summarized using descriptive statistics for patients who escape. 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. Patients who discontinued the study are considered as censored. Patients who were controlled until the end of the study will be censored at the last mUFC collection date. FAS will be used for this analysis.

The results of time-to-escape during treatment of osilodrostat up to Week 48 (secondary objective) were reported in the interim CSR, and will not be repeated for the final CSR. Time-to-escape up to end of study will be presented.

2.7.5 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 value and change from baseline to Week 12, Week 36 and Week 48, descriptive summaries were reported in the core CSR. Additional information from further visits including the extension period will be provided.

FAS will be used for this analysis.

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

For each of physical features of Cushing's disease: facial rubor, 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 scheduled visits will be

summarized. This includes the proportions of patients having a favorable shift from baseline to post-baseline time points. FAS will be used for this analysis.

2.7.7 Assess the change from baseline in bone mineral density by DXA scan

For bone mineral density measured by DXA scan at the lumbar spine and total hip, descriptive summaries of actual and percentage change from baseline to Week 48, Week 96 and EOT Extension will be provided by randomized treatment arm and for overall patients. FAS will be used for this analysis.

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

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 cortisol markers 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 arms and for all patients.

2.8 Safety 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, findings from Holter recordings, vital signs, and special tests) will also be presented.

In the Final CSR results for the overall study period will be analyzed using the SS. Safety analyses presented for the placebo-control period in the interim CSR will not be repeated. Safety analyses for overall study period will focus solely on the safety of osilodrostat treatment. The analyses include the osilodrostat arm besides the placebo arm excluding placebo-control period, and overall patients (excluding safety data of placebo arm collected during placebo-control period).

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 31 days after last dose of study medication.

2.8.1 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 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. A separate listing including any suspected or confirmed SARS-Cov-2 infections will be provided.

AEs will be summarized by number and percentage of subjects having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A subject with multiple occurrences of an AE will be counted only once in the respective AE category. A subject with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event.

In AE summaries the primary system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their frequency in the osilodrostat arm.

The following adverse event summaries will be produced by treatment; overview of adverse events and deaths (number and % of subjects who died, with any AE, any SAE, any drug reductions/interruptions), AEs by SOC and PT, summarized by relationship (all AEs and AEs related to study treatment), seriousness (SAEs and non-SAEs), leading to treatment discontinuation, leading to dose interruption/adjustment, requiring additional therapy and leading to fatal outcome. In addition, for the summary of serious and non-serious adverse events the number of occurrences will be produced (an occurrence is defined as >1 day between start and prior end date of record of same preferred term).

Additional exploratory analyses may be done to assess the impact of COVID-19 pandemic on adverse event reporting.

2.8.1.1 Adverse events of special interest / grouping of AEs

Groupings of AEs of special interest consist of adverse events for which there is a specific clinical interest in connection with LCI699 treatment (i.e. where LCI699 may influence common mechanism of action responsible for triggering them) or adverse events which are similar in nature (although not identical). The list of AESIs is updated periodically after MedDRA update and/or review of accumulating trial data and defined in the eCRS (electronic Case Retrieval Strategy) in the DMS (Document Management System). The most up-to-date version of the CRS will be used at the time of analysis.

For each specified AESI, number (%) of participants with at least one event of the AESI occurring during on treatment period will be summarized together with the individual preferred terms in that grouping. In addition, number (%) of participants with at least one AESIs by maximum CTC grade, related AESIs, serious AESIs as well as action taken and outcome of the respective AESI will be summarized.

All adverse events of special interest will be listed.

2.8.1.2 Adverse events by time of onset

AEs will also be categorized by the time of onset, and seperate summaries shown for defined time periods of the study.

The time periods used will be

- Baseline to Week 12
- Week 12 to Week 24
- Week 24 to Week 36
- Week 36 to Week 48
- Week 48 to Week 60
- Week 60 onwards

The denominator for each time period will be the number of patients still on the study at the start of that period.These summaries will be reported for

- Adverse events of Special Interest, regardless of study drug relationship, by category and preferred term
- Adverse events of Special Interest with suspected study drug relationship, by category and preferred term

2.8.2 Deaths

All deaths (on-treatment and post-treatment) will be listed, post treatment deaths will be flagged.

2.8.3 Laboratory data

Laboratory data summaries will include all assessments available for the lab parameter collected no later than 30 days or safety follow-up whichever is later after the last study treatment administration date using data from all sources. All laboratory assessments will be listed and those collected later than 30 days after the last study treatment date will be flagged in the listings.

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 that are graded for both low and high values, summaries will be done separately and labeled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

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

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

For laboratory tests where grades are defined by CTCAE

- 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 grades to compare baseline to the worst and from baseline to the last post-baseline on-treatment value

For laboratory tests where grades are not defined by CTCAE ,

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

In addition, the following laboratory results will be summarized.

- Patients meeting categorical liver function test criteria, including Hy's Law criteria for liver injury (ALT or AST > 3 x ULN and TBIL ≥ 2 x ULN and ALP < 2 x ULN), eDISH plot may be provided as well

The following listings will be produced for the laboratory data:

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

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

ECG data will be presented as follows:

- Number and percentage of patients with clinically notable ECG values will be summarized.
- ECG evaluations for all patients with at least one abnormality will be listed.

The notable criteria for PR are

- > 200 ms post-baseline and ≤ 200 ms at baseline
- Increase > 25% compared to baseline to a post-baseline value > 200 ms

The notable criteria for QRS are

- > 110 ms post-baseline and ≤ 110 ms at baseline
- Increase > 25% compared to baseline to a post-baseline value > 110 ms

The notable criteria for QT and QTcF are

- > 450 ms at any post-baseline and ≤ 450 ms at baseline
- > 480 ms at any post-baseline and ≤ 480 ms at baseline
- > 500 ms at any post-baseline and ≤ 500 ms at baseline
- an increase from baseline > 30 ms at any post-baseline
- an increase from baseline > 60 ms at any post-baseline

For 24hr Holter assessment, all findings will be listed and notable finding will be summarized based on clinical review of the Holter ECG data using the following criteria

- Potentially related to QT (Ventricular extra beats ≥200/24h, Ventricular tachycardia, Non-sustained VT, Sustained VT, Ventricular fibrillation, Ventricular flutter, Syncope, Torsades de Pointes, Bradycardia < 40/min)
- Potentially related to conduction (New Left Bundle Branch Block, New Right Bundle Branch Block, Mobitz II AV block, Complete heart block Grade III)
- Other relevant arrhythmias (Atrial fibrillation, Atrial flutter)

2.8.4.2 Vital signs

All vital signs data (height (cm), weight (kg), body temperature (^{0}C), supine pulse rate (beats per minute), and supine systolic/diastolic blood pressure (mmHg)) will be listed by patient and visit/time, and abnormalities will be flagged on listing. For blood pressure, two measurements are planned to be taken and the average will be used for analysis purpose. Shift table based on notable value will be provided for vital signs. Change over time from baseline will be summarized.

The criteria for clinically notable abnormalities are defined as follows:

Clinically notable elevated values

- Systolic BP: ≥ 180 mmHg and an increase ≥ 20 mmHg from baseline
- Diastolic BP: ≥ 105 mmHg and an increase ≥ 15 mmHg from baseline.
- Supine pulse: ≥ 120 bpm with increase from baseline ≥15 bpm
- Weight: Increase from baseline of ≥ 10%

Clinically notable below normal values

- Systolic BP: ≤ 90 mmHg and a decrease ≥ 20 mmHg from baseline
- Diastolic BP: ≤ 50 mmHg and a decrease ≥ 15 mmHg from baseline
- Supine pulse: ≤ 50 bpm with decrease from baseline ≥ 15 bpm
- Weight: Decrease from baseline of ≥ 5%

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.

2.8.4.3 Tumor volume and longest dimension

For tumor volume evaluated by MRI (or CT) by central assessment of an independent neuroradiologist, descriptive summary of actual tumor volumes as well as its change from baseline will be provided at visits where evaluation is scheduled (Week 26, 48, 72, and 96). The independent neuroradiologist measured the tumor volume, when it cannot be easily distinguished, the whole pituitary gland was measured. For the analysis, only measurements of the tumor volume are used.

Patients with pituitary volume assessments at baseline will be monitored and measured at the pre-specified timepoints. Patients with no visibile or measurable pituitary tumour at baseline will be assessed at all timepoints whether a tumour becomes visible and it can be measured accordingly. Patients will be assessed whether the pituitary tumour is within or goes beyond the sella turcica at each time points of MRI assessmenst. Measurements and available information about new lesions of patients with only pituitary gland dimensions at baseline will be listed.

2.8.4.4 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 committed suicide, attempted suicide, done preparatory actions toward imminent suicidal behavior, suicidal ideation, and self-injurious behavior without suicidal intent will be summarized by treatment arm.

2.9 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 (see Section 5.4 for the score derivations). The FAS will be used for analyzing PRO data. No multiplicity adjustment will be applied.

Descriptive statistics will be used to summarize the actual and 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.

3 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.

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 ≥ 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%.

4 Change to protocol specified analyses

In the SAP for the core CSR, clarification is made that efficacy was summarized by randomized treatment arms during the placebo-control period and by randomized treatment arms and for overall patients during the open-label period. Safety was summarized by randomized treatment arms during the placebo-control period.

For the overall study period, only safety data associated with osilodrostat treatment was summarized, which means safety data in placebo-arm collected during placebo-control period was excluded from the analysis. The same approach will be followed for the final CSR.

5 Appendix

5.1 Imputation rules

Partial dates will remain partial in the data listings. For the purpose of analysis, the following imputation rules will be used to impute the partial dates.

5.1.1 Study drug

Any partial dates or gaps between dates should be resolved for analysis purpose. The end date of study drug is derived by using the last non-zero dose end date from the dose administration record CRF page. If after DBL the partial dates still exist for end date, the imputation rule is as below:

If month and year is present, but day is missing, set the end date to be the first day of the month. If after imputation of day, study medication end date is earlier then study medication start date set study medication end date to study medication start date.

5.1.2 AE date imputation

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 post-treatment period) will be listed and those collected during the pre-treatment and after 30 days of post- treatment period or safety follow-up whichever is later are to be flagged.

Any missing onset date, causality, or severity must be queried for resolution. Unsolved missing values will be imputed according to the following:

AE end date imputation:

1. If the AE end date month is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, 31DECYYYY, date of death).
2. If the AE end date day is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, last day of the month, date of death).
3. If AE year is missing or AE is ongoing, the end date will not be imputed.

AE start date imputation:

1. If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
2. If the AE start date year value is less than the treatment start date year value, the AE started before treatment. Therefore:
    a. If AE month is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).
    b. Else if AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).
3. If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore:
    a. If the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).
    b. Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

4. If the AE start date year value is equal to the treatment start date year value:
    a. And the AE month is missing the imputed AE start date is set to the AE reference start date + 1 day.
    b. Else if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).
    c. Else if the AE month is equal to the treatment start date month or greater than the treatment start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date.

5.1.3 Concomitant medication date imputation

The start/stop dates recorded in the electronic case report form (eCRF) will be used to identify when a concomitant medication or a significant non-drug therapy was taken during the study. Concomitant medications and significant non-drug therapies after the start of the study treatment will be listed and summarized by ATC class and standardized medication term for the Safety Set. These summaries will include medications starting on or after the start of study treatment or medications starting prior to the start of study treatment and continuing after the start of study treatment. Any prior medications and significant non-drug therapies starting and ending prior to the start of study treatment will be listed. These analyses will be based on Safety Set.
Any missing date will be queried for resolution. For any unsolved missing dates, the following rules in the following order will be applied to decide if a concomitant medication or a significant non-drug therapy was taken after the start of the study treatment and to decide if the data should be included in the summary table. Originally collected date will be listed in listings.
CM end date imputation:

1. If CM end day is missing and CM month/year are non-missing then impute CM day as the minimum of treatment end date and the last day of the month.
2. If CM end day/month are missing and CM year is non-missing then impute CM day as the minimum of treatment end date and the end of the year (31DECYYYY).
3. If CM day/month/year is missing then use the treatment end date + 1 day as the imputed CM end date.
4. If imputed CM end date is less than the CM start date, use the CM start date as the imputed CM end date.

1. CM start date imputation: If the CM start date year value is missing, the imputed CM start date is set to one day prior to treatment start date.
2. If the CM start date year value is less than the treatment start date year value, the CM started before treatment. Therefore:
    a. If the CM month is missing, the imputed CM start date is set to the mid-year point (01JulYYYY).

b. Else if the CM month is not missing, the imputed CM start date is set to the mid-month point (15MONYYYY).

3. If the CM start date year value is greater than the treatment start date year value, the CM started after treatment. Therefore:
    a. If the CM month is missing, the imputed CM start date is set to the year start point (01JanYYYY).
    b. Else if the CM month is not missing, the imputed CM start date is set to the month start point (01MONYYYY).
4. If the CM start date year value is equal to the treatment start date year value:
    a. And the CM month is missing or the CM month is equal to the treatment start date month, then the imputed CM start date is set to one day prior treatment start date.
    b. Else if the CM month is less than the treatment start date month, the imputed CM start date is set to the mid-month point (15MONYYYY).
    c. Else if the CM month is greater than the treatment start date month, the imputed CM start date is set to the month start point (01MONYYYY).

If complete (imputed) CM end date is available and the imputed CM start date is greater than the (imputed) CM end date, then imputed CM start date should be set to the (imputed) CM end date.

5.1.3.1 Prior events date imputation

Partial date of prior events (other than AE and CM) date imputation rules are as below:
If only day is missing then impute to be 15th of month. If both day and month are missing, then impute to June 30th. If entire date is missing then leave as missing. If after imputation, the date is after the first dosing date, then use the first dosing date.

5.1.3.2 Post events and therapies date imputation

Partial date of post events/therapies (other than AE and CM) date imputation rules are as below:
Start date:

- If Day is missing, then impute to the max (reference start date, first day of the month).
- Day and month are missing then impute to the max(reference start date, Jan 1)
- Reference start date will be last date of study treatment administration + 1.

End date: No imputation

5.2 AEs coding/grading

Adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. AEs are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1). The CTCAE grade of 5 (death) is not used; rather,

'fatal' is collected as AE outcome and death information is also collected on a separate eCRF page.

5.3 Laboratory parameters derivations

All laboratory values except FPG and HbA1c, will be converted into SI units and the severity grade calculated using appropriate common toxicity criteria (CTC).
As CTC only grades lab values as grade 1-4, grade 0 will be used when lab value is normal. A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.
If sites report WBC differential counts in percentage (%) with corresponding lab normal ranges in terms of %, the % differentials will be converted to absolute differentials as Absolute value = [Value (%)/100] x WBC.

5.4 Patient-reported outcomes scores

5.4.1 CushingQoL

The CushingQoL is a valid and reliable disease-specific QoL questionnaire which assesses health-related quality of life (HRQoL) in patients with Cushing's syndrome and has been validated in patients with Cushing's disease (Webb SM, 2008; Nelson L., 2013). The CushingQoL consists of questions reflecting dimensions of HRQoL related to physical aspects (e.g. 'I bruise easily'), psychological aspects (e.g. 'I am more irritable, I have sudden mood swings and angry outbursts'), and social aspects (e.g. 'I have had to give up my social or leisure activities due to my illness').
The questionnaire consists of 12 items measured on a five point Likert-type scale assessing how often ('always' to 'never') or how much ('very much' to 'not at all') each item has been related to the patient's Cushing's disease in the previous 4 weeks. Scoring of each item ranges from 1 ('Always' or 'Very much') to 5 ('Never' or 'not at all').

Patients who complete 9 or more items at an assessment are considered evaluable for that visit. Standardized scores can be calculated as follows:

The raw score is calculated by summing the individual item scores prior to being standardized so that the total score ranges from 0 to 100, with a lower score indicating a greater impact on HRQoL. The following formula can be used to calculate the total score:

$$[(X - L) / (H - L)] * 100$$

Where X is the total score of the subscale of interest, L is the lowest possible score of the subscale, and H is the highest possible score for the subscale.

Recent research recommends that a 2 sub-scale scoring (namely, a *psychosocial issues scale* and a *physical problems scale*) provides the optimal interpretation, rather than the total score.

(Tiemensma J. 2016). The CushingQoL 2 sub-scale scoring of each subscale is exactly the same as the total score. The items which comprise each subscale are shown in Table 5-1 below:

Table 5-1 Items for the two subscales of CushingQoL

Psychosocial issues subscale		Physical problems subscale	
2	*I have pain that keeps me from leading a normal life*	1	*I have trouble sleeping*
5	*I am more irritable, I have sudden mood swings and angry outbursts*	3	*My wounds take a long time to heal*
6	*I have less self-confidence, I feel more insecure*	4	*I bruise easily*
7	*I am worried about the changes in my physical appearance due to my illness*		
8	*I feel less like going out or seeing relatives or friends*		
9	*I had to give up my social or leisure activities due to my illness*		
10	*My illness affects my everyday activities such as working or studying*		
11	*It is difficult for me to remember things*		
12	*I am worried about my health in the future*		

5.4.2 BDI-II

The BDI-II is a patient-reported instrument developed to measure the severity of depression in adults and adolescents aged 13 years and older. The BDI-II is designed to be completed by the patient on paper and takes approximately five minutes to complete. The BDI-II comprises 21-items assessing the common cognitive symptoms of depression over the previous two weeks Items are rated on a four-point severity scale of 0 (‘not at all’) to 3 (‘extreme’ form of each symptom) with differing response options for each item. A global score ranging from 0 to 63 is calculated with a higher score representing a greater level of depression.

The following scoring guidelines for interpretation of the BDI-II have been suggested (Smarr, 2011):

Minimal range = 0-13

Mild depression = 14-19

Moderate depression = 20-28

Severe depression = 29-63

A minimal clinically important difference for improvement in BDI-II scores has been reported as a 17.5% reduction in scores from baseline; however, this is dependent on baseline severity (Button Ks, 2015)

5.4.3 EQ-5D-5L

Health status will be assessed using the EQ-5D-5L. The EQ-5D-5L has two components, the EQ-5D-5L descriptive system and the EQ-5D-5L visual analog scale (VAS) (Herdman, M., 2011, The EuroQoL Group, 2013). The EQ-5D-5L descriptive system comprises the following

five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five levels: 'no problems', 'slight problems', 'moderate problems', 'severe problems' and 'unable to do activity or extreme problems'. A utility index can be computed from the EQ-5D-5L descriptive system with utility scores ranging from -0.281 (worst imaginable health state) to 1 (best imaginable health state), with -0.281 representing an "unconscious" health state. The EQ-5D-5L VAS records the subject's self-rated health state on a 100-point vertical VAS (0=worst imaginable health state; 100=best imaginable health state) (The EuroQoL Group, 1990) A score difference of 0.037-0.069 for the EQ-5D-5L utility score will be used as MID (McClure, 2017). A score difference of 7 for the EQ-5D-5L VAS will be used as MID estimates for the EQ-5D-5L (Pickard, 2007).

The relevant scoring algorithm will be applied to patient-level data in order to derive EQ-5D -5L index-based scores. The United Kingdom Measurement and Valuation of Health study value set is generally considered the base case scoring function for the purposes of publication (Dolan 1997). Therefore, the EQ-5D-5L utility scores will be based on United Kingdom values for reporting in the CSR. An example of calculating the utility index from raw scores on the EQ-5D-5L are shown below:

Table 5-2 Illustration of calculating the utility index from raw score on the EQ-5D-5L

	Central estimate	Standard Deviation	Value for health state 23245
Constant	1.000		1.000
Mobility			
slight	0.051	0.004	0.051
moderate	0.063	0.004	
severe	0.212	0.006	
unable	0.275	0.006	
Self-care			
slight	0.057	0.004	
moderate	0.076	0.004	0.076
severe	0.181	0.005	
unable	0.217	0.005	
Usual activities			
slight	0.051	0.004	0.051
moderate	0.067	0.004	
severe	0.174	0.005	
unable	0.190	0.005	
Pain/discomfort			
slight	0.060	0.004	
moderate	0.075	0.005	
severe	0.276	0.007	0.276
extreme	0.341	0.008	
Anxiety/depression			
slight	0.079	0.004	
moderate	0.104	0.005	
severe	0.296	0.007	
extreme	0.301	0.007	0.301
Probability (group 1)	0.397	0.019	0.397x0.427+0.270x0.939+0.333x1.635
Probability (group 2)	0.270	0.018	=0.9675
Probability (group 3)	0.333	0.018	
Slope (group 1)	0.427	0.031	
Slope (group 2)	0.939	0.067	
Slope (group 3)	1.635	0.017	
The value for health state 23245			1-0.9675x(0.051+0.076+0.051+0.276+0.301) =0.270

6 Reference

American Diabetes Association, (2010), 'Diagnosis and Classification of Diabetes Mellitus', Diabetes Care, 33, Supplement 1, S62-S69.

Button KS, Kounali1 D, Thomas N, Wiles NJ, Peters TJ, Welton NJ, Ades AE, and Lewis G (2015), Minimal clinically important difference on the Beck Depression Inventory – II according to the patient's Perspective, Psychological Medicine, 45: 3269–3279.

Dolan P (1997), Modeling valuations for EuroQol health states, Med Care, 35:1095-108.

Herdman, M., Gudex, C., Lloyd, A., Janssen, M. F., Kind, P., Parkin, D., ... & Badia, X. (2011), Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L), *Quality of life research*, *20*(10): 1727-1736.

McClure, Nathan S., et al. (2017), "Instrument-defined estimates of the minimally important difference for EQ-5D-5L index scores", Value in Health, 20.4: 644-650.

Nelson LM, Forsythe A, McLeod L et al (2013), 'Psychometric evaluation of the Cushing's Quality of Life Questionnaire', The Patient: 6, No. 1: 1-14.

Norman GR, Sloan JA, Wyrwich KW (2003) Interpretation of changes in health-related quality-of-life: the remarkable universality of half a standard deviation. Med Care; 41:582-92.

Pickard AS, Neary MP, Cella D (2007), Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer, Health Qual Life Outcomes, 5:70.

Smarr, K.L. & Keefer, A.L. (2011), Measures of Depression and Depressive Symptoms, Arthritis Care and Research Vol. 63, No. S11: pp S454–S466

Smith B, Vandenhende F, DeSante K, et al (2000), 'Confidence interval criteria for assessment of dose proportionality', Pharmaceutical research, 17, No 10

The EuroQol Group. EQ-5D-3L User Guide. 2013. Available at: URL:

https://www.euroqol.org/about-eq-5d/publications/use-guide.html Accessed Jul 26, 2017.

The EuroQol Group. EuroQol-5D: a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199-208

Tiemensma, J., Depaoli, S., & Felt, J. M. (2016), Using subscales when scoring the Cushing's quality of life questionnaire, European journal of endocrinology, 174(1): 33-40

Webb SM, Badia X, Barahona MJ, Colao A, Strasburger CJ, Tabarin A, van Aken MO, Pivonello R, Stalla G, Lamberts SWJ et al (2008), Evaluation of health-related quality of life in patients with Cushing's syndrome with a new questionnaire, European Journal of Endocrinology, 158: 623–630. (doi:10.1530/EJE-07-0762)