NOVARTIS

Clinical Development

Osilodrostat (LCI699)

CLCI699C1201 / NCT02468193

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

RAP Module 3 – Detailed Statistical Methodology

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Document History – Changes compared to previous version of RAP module 3

Version	Time point	Date	Changes
1.0	Prior to DB lock	9-Sep-2015	Initial version
Amendment 1.0	Prior to DB lock	19-Jan-2017	1. Section numbers were updated as previous version had section 7.3 for both PK and efficacy sections erroneously. Section numbers of subsequent sections were also updated. 2. In order to make summaries consistent with internal guideline as much and also reflect the recent protocol amendment, following changes are incorporated in the analysis plan: • Section 5 Data cutoff for analysis Clarified that all assessments prior to data cut off will be included in the analysis. • Section 7.1.3 Demography and baseline disease characteristics 25th and 75th percentiles will not be presented to be consistent with standard Baseline height and weight are added in the demography table. • Section 7.3 Efficacy evaluation Described all efficacy listings will be presented by type of disease. • Section 7.3.1.1 Supportive analyses Clarified summary of change from baseline in mUFC by subgroup of prior experience of metyrapone will be presented when at least 4 subjects are included in either group. • Section 7.3.2.1 Response rate Clarified that intention of 95% presentation in summary of response rate is not for statistical summary in this small study. In addition, this will be presented only when at least 4 subjects have been enrolled and stayed in the study through week 12. • Section 7.5.1.4 Safety disclosure is newly inserted. • Section 7.5.2.1 Hematology, chemistry, urinalysis, coagulation and thyroid panel A Typo in equation of corrected serum calcium was corrected.

Version	Time point	Date	Changes
			Clarified that all data up to data cut-off will be used for the on-treatment summary. • Section 7.5.3 Vital signs Only absolute change will be summarized to be consistent with oncology standard instead of absolute and percent change from baseline. Clarified that abnormal values will be flagged in the listing. Table 7-2 clinically notable abnormal values is updated to be consistent with oncology standard. • Section 7.5.4 Electrocardiogram (ECG) Summary table is modified to be consistent with internal oncology standard and Table 7-3 is modified with new category. 3. Section 8.6 Imputation rules for partial or missing dates is moved to newly created appendix 2. Moreover, imputation method is modified to be consistent with oncology standard. 4. Section 8.6 Assessment time window is inserted for efficacy and safety. 5. Section 9 Changes from planned analysis in the study protocol is updated with changes listed in the above.
Amendment 2.0	Prior to DB lock	27-Sep-2017	1. Administrative change in change history by adding a column for time point. In addition, cosmetic corrections are made across documents. 2. Section 2 Study design – Description has been updated for the end of optional extension period (after week 48) of the study. 3. Sections 7.1 patient studied and 7.2 study medication – listing will be by disease type in similar to efficacy and safety. 4. Section 7.1.3 demography and baseline disease characteristics • Remove the description of metyrapone as for the use of previous medication, as another medication may have been used.

Version	Time point	Date	Changes
			• Clarified best response to the previous medication is listed. [redacted] 5. Section 7.2.1 exposure of study treatment – Inserted how to handle multiple different doses are given in a certain schedule. 6. Section 7.3 efficacy evaluation – Clarified that AIMAH and PPNAD will be presented, respectively, and will not be grouped together for listing by subtype of Cushing's syndrome. 7. Section 7.3.2.3 – section title has been updated to change from baseline in ACTH and other adrenal steroid hormones 8. Section 7.5 Safety evaluation • Listing will be sorted by subtype of Cushing's syndrome in similar to efficacy listing. • The definition of the on-treatment period is clarified as date from first dose of study medication through 30 days after last dose of study medication, regardless of another therapy use for Cushing's syndrome. • Section 7.5.1 Adverse events – Link to NCI CTCAE version 4.03 is removed as the analysis preparation is based on the internal guidance of EASE (**E**nd to end **a**nalysis **s**tandards from protocol to r**e**porting) which is based and modified on CTCAE version 4.03. • Section 7.5.2.1 hematology, chemistry, urinalysis, coagulation and thyroid panel is modified that WBC differentials will be based on absolute values when only percentage values are collected in alignment with standard methodology internally.

Version	Time point	Date	Changes
			[redacted]
Amendment 3.0	Prior to DB lock	22-Jun-2018	1. Administrative changes: • Section 9 Changes from planned analysis in the study protocol – typos are corrected. • Typos are corrected across document with Safety analysis set. 2. Section 6.1.3 Pharmacokinetic analysis set (PAS) – Clarified the conditions further regarding time window allowance and missing incident dose. 3. Section 7.1.2 Patient disposition – removed the wording of Week 96 restriction in the optional extension period. 4. Section 7.2.1 Exposure to study treatment – derivation for dose with longest duration • Analysis set is corrected o SAS and added in the section 9 change from planned analysis as well. • It was inconsistent descriptions between this document and TFL shells about how to handle multiple doses with the longest. duration, which is now consistently to choose the highest dose rather than average dose. • Clarified that sum of durations will be summarized at different occasions for a given dose. 5. Section 7.3 Efficacy evaluation • Section 7.3.1 Primary efficacy analysis – clarified that corresponding 95% CI will be presented for both mean change and mean % change. • Section 7.3.2.1 Response rate – clarified that denominator of response rate after study period II will be based on patients who entered into study period II and reached at a specific visit. • Section 7.3.2.2 change from baseline in serum cortisol - clarified that corresponding 95% CI will be presented for both mean change and mean % change.

Version	Time point	Date	Changes
			6. Section 7.4 Pharmacokinetic evaluation – Corrected to clarify graphical depiction over time will be performed by week 12 dose and visit. 7. Section 8.6 Assessment window – Clarified that an unscheduled assessment may be used as an alternative assessment for safety summary by visit.

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Table 1-1 List of abbreviations

abbreviations	Meaning
ACTH	Adrenocorticotropic Hormone
AE	Adverse event
AIMAH	ACTH-Independent Macronodular Adrenal Hyperplasia
BDI-II	Beck Depression Inventory-II
b.i.d.	*bis in diem*/twice a day
BMI	*Body mass index*
CD	Cushing's disease
CREDI	Clinical Research Documentation and Information system
CS	Cushing's syndrome
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DAR	Drug administration record (CRF page)
ECG	Electrocardiogram
FAS	Full analysis set
(m)UFC	(mean) Urine Free Cortisol
LLOQ	Lower limit of quntitation
MedDRA	Medical Dictionary for Regulatory Activities
PAS	Pharmacokinetic analysis set
PD	Pharmacodynamics
PDs	Protocol deviations
PK	Pharmacokinetic
PPNAD	Primary Pigmented Nodular Adrenal Dysplasia
SAS	Safety analysis set
SSD	Study specific documentation

1 Introduction

This document describes the planned statistical analysis and methodology for study LCI699C1201 CSR in patients with Cushing's syndrome (CS).

Data will be analyzed according to the data analysis section 10 of the study protocol, which is available in Appendix 16.1.1 of the CSR. Important information is given in the following sections and details are provided, as applicable, in Appendix 16.1.9 of the CSR.

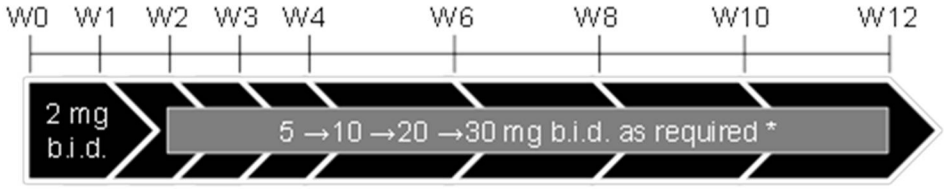
2 Study design

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

Study period I (Week1 to Week 12):

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

Figure 2-1 Study period 1



* Dose can be down titrated to 1 mg b.i.d. if needed

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

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

Study period II (Week 12 to Week 48):

Study period II is the period to assess the sustainability of efficacy and to assess long-term safety. For this study period II, only the patients who tolerate and agree to continue osilodrostat

treatment will continue study treatment during period II. The patient will be administered with the stable therapeutic dose, which will be achieved in the study period I. The dose level could be modified according to the patient condition (refer to [Sections 6.1 and 6.3 of the study protocol]. The mUFC will also be measured to evaluate the efficacy in this period.

Optional extension period (after Week 48):

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

The patient will continue to receive stable therapeutic dose. The dose level could be modified according to the patient condition.

Follow-up

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

3 Objectives

3.1 Primary objective

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

3.2 Secondary objectives

The secondary objectives are as follow:

- To assess the percent change from baseline in the mUFC at the individual patient level at Week 24 and Week 48.
- To assess the absolute and percent change from baseline in mUFC at Week 12, Week 24 and Week 48.
- To assess the complete, partial, and overall response rate at Week 12, Week 24 and Week 48.
- To assess the absolute and percent change from baseline in morning serum cortisol at the individual patient level at Week 12, Week 24 and Week 48.
- To assess the absolute and percent change from baseline in morning serum cortisol at Week 12, Week 24 and Week 48.
- To assess the absolute and percent change from baseline in steroid hormones at the individual patient level at Week 12, Week 24 and Week 48.
- To assess the change from baseline in cardiovascular-related metabolic parameters associated with CS at Week 12, Week 24 and Week 48.
- To assess the general safety of osilodrostat.

- To assess the change from baseline in Patient-Reported Outcome (Health Related Quality of Life) at individual patient level at Week 12, Week 24 and Week 48.
- To evaluate PK of osilodrostat in patients with CS.

4 Sample size and power considerations

4.1 Sample size calculation

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

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

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

4.2 Power for analysis of primary and secondary variables

Not applicable.

5 Data cutoff for analyses

The study will be analyzed at least 3 times, at completion of study period I (Week 12), at completion of study period II (Week 48), and at the final analysis after all patients complete the study. The initial analysis will be performed when all enrolled patients have completed the dose titration period of study (study period I) or have prematurely withdrawn from the study, whichever comes first. All assessments and/or events occurred on or prior to data cut off will be included in the analysis.

A patient who didn't enter into study period II (After Week 12 through Week 48) or optional extension phase (after Week 48) will not be considered withdrawn from study. A patient in study period II or in optional extension phase will be analyzed in a report once the patient completed the period or discontinued earlier.

6 Analysis sets

6.1.1 Full Analysis Set

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

6.1.2 Safety Analysis Set

The safety analysis set (SAS) includes all patients who received at least one dose of osilodrostat and had at least one valid post-baseline safety assessment. Post-baseline safety assessments include all assessments for safety endpoints including laboratory, ECG, vital signs and adverse events (AE)/SAEs.

6.1.3 Pharmacokinetic analysis set

The pharmacokinetic analysis set (PAS) consists of all patients who received at least one dose of osilodrostat and had at least one evaluable PK concentration at any visit (post-first-dose). A PK concentration may be considered non-evaluable as per scientific judgement of the clinical pharmacology expert and the reason of being non-evaluable will be documented.

Data that is considered non-evaluable including, but not limited to, by the below reasons will be flagged and excluded from the analysis set.

- The patient didn't receive the incident dose (last dose administered prior to PK collection) as planned per protocol, OR
- PK concentration data after vomit occurring within 4 hours of dosing, OR
- If the elapsed time between PK sample and prior dose didn't fall within acceptable window.
    - Pre-dose samples within 0.5h before dose administration, and within 9h to 15h after the previous dose.
    - Post-dose samples with elapsed time window within protocol specified nominal time range (i.e. within 0.25h to 0.75h, 1h to 2h and 3h to 4h).

7 Statistical analyses

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 before publication or presentation.

7.1 Patients studied

Summary statistics of data pertaining to subject disposition, demographics, baseline characteristics, medical history, prior medications and protocol deviations will be tabulated and displayed using grouping described below.

All listings will be generated by type of disease (ectopic corticotropin syndrome, adrenal adenoma, adrenal carcinoma, AIMAH and PPNAD) for full analysis set, unless otherwise specified.

7.1.1 Grouping for analyses

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

Data will be summarized only by a single arm name osilodrostat, as the level of dose administration will be adjusted depending on a subject response, which will be closely monitored by an investigator for safety/tolerability, and efficacy (expected dose level from 2 mg b.i.d to 30 mg b.i.d).

7.1.2 Patient disposition

For overall study period as well as each period, counts of patients for the following items will be summarized for the Full analysis set:

- The number of patients who discontinued at any time and primary reason for discontinuation at any time
- The numbers of patients who entered into the Study period I (Day 1 to Week 12)
- The numbers of patients who entered into the Study period II (Week 12 to Week 48)
- The numbers of patients who entered into the Optional extension period (after Week 48)

A patient who did not enter into study period II (After Week 12 through Week 48) or optional extension phase (after Week 48) will not be counted as discontinuations in the corresponding period.

7.1.3 Demography and baseline disease characteristics

All demographic will be summarized and listed in detail for the Full analysis set. Categorical data will be summarized by frequencies and percentages. For continuous data, mean, standard deviation, minimum, median and maximum will be presented. Demographic variables include Age (in year), Age (< 65 years/≥ 65 years), gender, race, ethnicity, baseline height, weight and BMI.

Baseline disease characteristics will be listed, including diagnosis date of Cushing's syndrome, cause of disease (ectopic corticotropin syndrome, adrenal adenoma, adrenal carcinoma, AIMAH/PPNAD), use of previous medication and the best response to the previous medication, Cushing's syndrome status (de novo or persistent/recurrent) and previous surgery.

For a patient with ectopic corticotropin syndrome, primary site of cancer, date of initial diagnosis and metastatic sites will be presented in a listing.

7.1.4 Medical history

Relevant medical history and ongoing medical conditions will be listed for the Full analysis set.

7.1.5 Prior medication

Prior medication, prior radiation and prior surgery for Cushing's syndrome will be listed for the Full analysis set.

7.1.6 Protocol deviations (PDs)

All CSR-reportable PDs up to data cutoff will be listed. The criteria for CSR-reportable protocol deviation are specified in the study specific documentation (SSD) and will be finalized prior to database lock.

7.2 Study medication

All listings will be generated by type of disease (ectopic corticotropin syndrome, adrenal adenoma, adrenal carcinoma, AIMAH and PPNAD), unless otherwise specified.

7.2.1 Exposure to study treatment

The exposure to study drug will be summarized overall and listed for the safety analysis set. Duration of exposure (weeks) will be calculated as the earliest of (date of last administration of osilodrostat, date of data cut-off, date of death) minus date of first osilodrostat administration plus one. If drug administration is temporarily interrupted for a certain period, it is included in the calculation of duration.

The highest dose (mg/day), average dose (mg/day), and the dose with the longest duration of administration (mg/day) up to Week 12 and up to data cut-off will be summarized. For dose with the longest duration, the highest dose will be used if there are more than one dose with the same longest duration, and the sum of durations should be used if multiple different occasions are observed for a given dose. If multiple different doses are given in a certain period for a patient (e.g. 2 mg/day on Day 1 + 3 mg/day on Day 2), then daily dose for the period will be the mean of doses, but the detailed information will be presented in a listing.

Drug administration record (DAR) will be kept on the CRF DAR page along with details regarding dose interruption, dose reduction, and dose increase along with the reason for dose modification. This information will be listed with the mUFC information.

7.2.2 Concomitant medication

Concomitant medications and significant non-drug therapies will be listed and summarized using frequency counts and percentages by ATC class and preferred term overall regardless of study period.

If the start date of a concomitant medication is missing, then it will be assumed to have the medication administered started on or after the first dose of study treatment.

7.3 Efficacy evaluation

All efficacy analyses will be performed for full analysis set. All listings will be generated by type of underlying disease (ectopic corticotropin syndrome, adrenal adenoma, adrenal carcinoma, AIMAH and PPNAD) for full analysis set, unless otherwise specified.

7.3.1 Primary efficacy analysis

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

The primary endpoint is the percent change from baseline in mUFC at the individual patient level. Due to the limited sample size and variabilities of patients, no statistical hypothesis is set up for this study. The percent and absolute change will be plotted over time along with dose administration data by individual patient for the Full analysis set. For patients who discontinued prior to Week 12, data will not be imputed and only actual data will be presented. Additionally, mean change and mean % change will be summarized along with corresponding 95% CIs.

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

7.3.1.1 Supportive analyses

Summary tables of overall mean change from baseline and the mean percent change from baseline in mUFC will be generated at Week 12, Week 24 and Week 48, descriptively for all patients. In addition, these parameters will be presented by status of prior treatment with metyrapone. Summary by the status of prior treatment with metyrapone will be presented, if at least 4 patients are included in either group (patients with prior treatment with metyrapone or patients without prior treatment with metyrapone).

7.3.2 Secondary efficacy analysis

There is no key secondary endpoint pre-specified in this study. All secondary endpoints are to support individual patient response to osilodrostat.

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

Point estimates of complete, partial and overall response rates will be presented with exact 95% confidence interval (Clopper-Pearson method) at Week 12 (end of study period I), Week 24 and Week 48 (end of study period II), respectively, for the Full analysis set. Complete response (CR) rate is defined as the proportion of enrolled patients who have mUFC $\leq$ ULN. Partial response (PR) rate is defined as the proportion of enrolled patients who have mUFC>ULN and at least 50% reduction from baseline in mUFC. Overall response rate (ORR) is defined as the proportion of enrolled patients with mUFC $\leq$ ULN or at least 50% reduction from baseline.

Complete response at Week 12 is defined as a patient with mUFC≤ ULN at Week 12. A patient with missing mUFC assessment at Week 12 or a patient who discontinued study drug during study period I will be counted as a non-responder for the analysis.

Similarly, complete response at Weeks 24 or Week 48 is defined as a patient with mUFC≤ ULN at Week 24 or Week 48, respectively). A patient who entered into study period II and reached at a specific visit will be included in the denominator of the calculation of response rate at the visit. If a patient who entered into the period discontinued study drug prior to mUFC assessment or had missing mUFC at the time of assessment, the patient will be considered a non-responder.

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Please note that the purpose of presentation of 95% CI is not for statistical inference in this small study. Moreover, this summary will be presented only when at least four subjects have been enrolled overall and stayed in the study through week 12.

7.3.2.2 Change from baseline in serum cortisol

Morning serum cortisol will be assessed at central laboratory. The percent change from baseline in morning serum cortisol along with dose administration data will be plotted over time for each patient. Additionally, a descriptive summary of the mean change from baseline and the mean percent change from baseline in morning serum cortisol will be provided at Week 12, 24 and 48. The corresponding 95% CIs will be provided in both mean change and mean % change.

Additionally serum cortisol will be assessed by local laboratory. These will be presented in a listing only.

7.3.2.3 Change from baseline in ACTH and other adrenal steroid hormones

Both mean change and mean percent changes from baseline in the following ACTH and adrenal steroid hormones will be listed over time by individual patient: plasma adrenocorticotropic hormone (ACTH), serum aldosterone, 11-deoxycorticosterone, 11-deoxycortisol, testosterone and estradiol.

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

The mean change and mean percent change from baseline in the following cardiovascular related metabolic parameters will be provided in a listing: Fasting glucose, HbA1c, fasting lipid profile, blood pressure, body weight body mass index (BMI) and waist circumference. BMI will be calculated as weight (kg)/ [height (m)]^2 using the baseline weight and height.

7.3.3 Other efficacy analysis

Not applicable.

7.4 Pharmacokinetic evaluation

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

As sparse pharmacokinetic sampling is performed in this study, traditional non- compartmental analysis will not be performed to calculate pharmacokinetic parameters. Plasma concentration data of osilodrostat will be listed by subject, visit, incident dose and nominal sampling times. Descriptive statistics of plasma concentrations will be provided by incident dose, visit and nominal sampling times. Graphical depiction (mean and individual) for osilodrostat concentrations over time during the course of the study will be performed by Week 12 dose and visit. When Week 12 dose level is missing for a subject with an early withdrawal or temporary interruption, then corresponding patient data will not be plotted.

7.4.1.1 Data handling principles

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

7.4.3 Patient-reported outcomes

The Cushing's Disease Health-Related Quality of Life Questionnaire (CushingQoL) score is identified as the primary patient reported outcome variable of interest. Beck Depression Inventory-II (BDI-II) total score is identified as secondary PRO variables of interest.

For CushingQoL, details for data handling and how to calculate standard scores are discussed in the Appendix 1. The score can be interpreted if the number of unanswered items does not exceed 3 (25% of the questions). If the number of unanswered items exceed 3, then the sum of total score and standardized score will not be calculated.

For BDI-II, each of 21 items corresponds to a symptom of depression and the sum of total score will be calculated where each item has a four-point scale ranging from 0 to 3, leading to a total score from zero to 63. Interpretation of the total score is described at the end of the questionnaires: score of 1 to 10 is considered normal, score of 11 to 16 is considered mild mood disturbance, score of 17 to 20 is considered borderline clinical depression, score of 21 to 30 is considered moderate depression, score of 31 to 40 is considered severe depression and score of over 40 is considered extreme depression.

No imputation will be applied if the total scores are missing at a visit. All available data of raw scores and sums of scores for both questionnaires as well as standardized scores for

CushingQoL until completion or early discontinuation during study period I and II will be listed only due to very small sample size.

7.5 Safety evaluation

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

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

1. pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
2. on-treatment period: from day of first dose of study medication to 30 days after last dose of study medication, regardless of another therapy used for Cushing's syndrome (e.g. metyrapone)
3. post-treatment period: starting at day 30+1 after last dose of study medication

Unless otherwise specified, summary tables present data during on-treatment period in addition to baseline data. In listings, all data will be presented regardless of observation period and will be presented by type of disease (ectopic corticotropin syndrome, adrenal adenoma, adrenal carcinoma, AIMAH and PPNAD) for safety analysis set, unless otherwise specified.

7.5.1 Adverse events

Summary tables for ***treatment-emergent*** adverse events (AEs) will include AEs that started or worsened during the on-treatment period. However, all 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 are to be flagged.

Adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The latest version available at the time of database lock will be used.

AEs will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

The CTCAE represents a comprehensive grading system for reporting acute and late effects of cancer treatments. CTCAE v4.03 is graded by definition by a 5-point scale generally corresponding to clinical severity (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).

For adverse events for which CTCAE grades are not available, grades 1 – 4 corresponding to the severity of mild, moderate, severe, and life threatening will be used. CTCAE grade 5 (death) is not used in this study; rather, this information will be collected on the "End of Treatment" or "Study evaluation completion" eCRF pages.

7.5.1.1 General rule for AE reporting

AE summaries will include all AEs starting on or after study day 1 (i.e. on or after the day of the first administration of study drug) but no later than data cutoff or study withdrawal of each

patient, whichever comes first. All AEs before data cutoff date will be listed, including those that start before study day 1. AEs starting prior to study day 1 will be identifiable based on the AE start date displayed in the listings and not summarized in tables.

AEs will be summarized by presenting the number and percentage of patients having at least one AE, and having at least one AE in each body system/primary system organ class and for each preferred term using the most current MedDRA coding available prior to database lock and maximum CTC grade. A subject with multiple occurrences of an AE will be counted only once in the AE category. A patient with multiple CTC grades for an AE will be summarized under the maximum CTC grade recorded for the event. AEs with missing CTC grade will be summarized under "missing".

Any information collected (e.g. CTC grades, relationship to study drug, action taken etc.) will be listed as appropriate.

7.5.1.2 AE summaries

The following adverse event summaries will be produced:

- Adverse events, regardless of study drug relationship, by primary system organ class, preferred term and maximum CTC grade (Any or Grade 3/4)
- Adverse events, with suspected study drug relationship, by primary system organ class, preferred term and maximum CTC grade (Any or Grade 3/4)
- On treatment deaths, by primary system organ class and preferred term
- Serious adverse events, regardless of study drug relationship, by primary system organ class, preferred term and maximum CTC grade (Any or Grade 3/4)
- Serious adverse events with suspected study drug relationship, by primary system organ class, preferred term and maximum CTC grade (Any or Grade 3/4)
- Adverse events leading to study drug discontinuation, regardless of study drug relationship, by primary system organ class and preferred term
- Adverse events requiring dose adjustment or study-drug interruption, regardless of study drug relationship, by primary system organ class and preferred term
- Adverse events requiring additional therapy, regardless of study drug relationship, by primary system organ class and preferred term

7.5.1.3 AE of special interest

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 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 an internal repository system named CREDI (Clinical Research Documentation and Information system) 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.

Following summaries will be produced:

- Adverse events of special interest, regardless of study drug relationship, by group name, preferred term, and maximum CTC grade (Any or Grade 3/4)
- Adverse events of special interest with suspected study drug relationship, by group name, preferred term, and maximum CTC grade (Any or Grade 3/4)

7.5.1.4 Safety disclosure

For the legal requirements of ClinicalTrials.gov, two required tables on on-treatment adverse events which are not serious adverse events and on on-treatment serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety analysis set population.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective.

7.5.2 Laboratory abnormalities

For analyzing laboratory results, data from all sites will be combined and reported. Table 7-1 provides the local laboratory information except for serum cortisol, which will be assessed by both local and central laboratories and reported, respectively.

Eligible laboratory data will be converted into values in SI units and classified into CTC grades according to NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.03. In the unlikely case, a local laboratory normal range overlaps into the higher (i.e. non-zero) CTC grade, if the laboratory value is within local normal limits it will be assigned a CTC grade of zero.

Table 7-1 Local clinical laboratory parameters

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, WBC Morphology with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)
Chemistry	Albumin, Alkaline phosphatase, ALT (GPT), AST (GOT), Bicarbonate, Glucose, Calcium, Chloride, Creatinine, Creatine kinase, GGT, Lactate dehydrogenase (LDH), inorganic phosphorus, lipase, amylase, magnesium, potassium, sodium, Total Bilirubin, Direct Bilirubin, Indirect Bilirubin, Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid
Urinalysis	Macroscopic Panel (Dipstick) (Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, pH, Protein, Specific Gravity,)
Coagulation	Prothrombin time (PT) or INR, Activated partial thromboplastin time (APTT)
Thyroid Panel	Serum TSH, free T4
Additional tests	Serum cortisol Pregnancy test (serum / urine) Fasting serum insulin and HbA1C LH, FSH Serum Type I collagen cross-linked N-telopeptide (NTX) and Serum bone-specific alkaline phosphatase (BAP)

7.5.2.1 Hematology, chemistry, urinalysis, coagulation and thyroid panel

The summaries will include all on-treatment laboratory assessments up to data cut-off date. All laboratory assessments will be listed with corresponding CTC grades and/or normal ranges. Both tables and listings will be presented for Safety analysis set.

For WBC differentials provided in percentage unit, values will be converted to absolute values with the below equation for grading including calculations of upper limit normal (ULN) and lower limit normal (LLN) as well: WBC differential count = (WBC count) × (WBC differentials percentage values/100).

For grading of serum calcium, values will be adjusted for albumin by the following equation:
Corrected serum calcium (mg/dL) = total calcium (mg/dL) – 0.8 [albumin (g/dL)-4]

The following summaries will be presented:

- Shift to the worst post-baseline up to data cut-off from baseline on CTC grade
- Number and percentage of 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). Each patient will be counted only for the worst grade observed post-baseline. All data up to data cut-off will be used.

7.5.2.2 Additional tests

Additional test information is listed in Table 7-1. Absolute and percent changes in these parameters will be listed over time, which include fasting serum insulin, HbA1c, luteinizing hormone (LH), follicle stimulating hormone (FSH) and bone metabolism markers (serum

Type I collagen crosslinked N-telopeptide (NTX) and serum bone-specific alkaline phosphatase (BAP)) . All other test results will be listed over time only for the Safety analysis set.

7.5.3 Vital signs

All vital signs data (height (cm), weight (kg), waist circumference (cm), body temperature (°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. Summary statistics of absolute change from baseline will be presented over time.

The criteria for clinically notable abnormalities are defined in Table 7-2 below. Abnormal values will be flagged in the listing.

Table 7-2 clinically notable abnormal values

	Abnormal criteria
Systolic BP (SBP) (mmHG)	≥ 180 mmHg and an increase ≥ 20 mmHg from baseline
	≤ 90 mmHg and a decrease ≥ 20 mmHg from baseline
Diastolic BP (DBP) (mmHG)	≥ 105 mmHg and an increase ≥ 15 mmHg from baseline
	≤ 50 mmHg and a decrease ≥ 15 mmHg from baseline
Supine pulse (bpm)	≥ 100 bpm with increase from baseline > 25 %
	≤ 50 bpm with decrease from baseline > 25 %
Weight (kg)	Increase from baseline of ≥ 10%
	Decrease from baseline of ≥ 10%
BMI (kg/m2)	<18.5 kg/m2
Waist Circumference (cm)	N.A.

7.5.4 Electrocardiogram (ECG)

Local 12-lead ECG evaluations will be listed with abnormality flag following criteria below in Table 7-3, regardless of scheduled/unscheduled assessments. The number and percentage of subjects with notable ECG will be presented up to week 12 and up to data cut-off, respectively. No imputation of missing data will be performed.

Table 7-3 ECG notable abnormal values

	Abnormal criteria
QT and QTcF (msec)	Increase from baseline > 30 to ≤ 60 (msec)
	Increase from baseline > 60 (msec)
	New >450 and ≤480 (msec)
	New >480 and ≤500 (msec)
	New >500 (msec)
Heart rate (beat per minute)	Decrease from baseline > 25% and post-baseline assessment < 50 (bpm)
	Increase from baseline > 25% and post-baseline assessment > 100 (bpm)

	Abnormal criteria
PR interval (msec)	Increase from baseline > 25% and post-baseline assessment > 200 (msec)
	New > 200 (msec)
QRS duration (msec)	Increase from baseline > 25% and post-baseline assessment > 120 (msec)
	New >120 (msec)

Separately, if there are abnormalities, local data will be transferred to central laboratory for re-read and adjudication by central laboratory, which will be listed separately. In addition, 24-hour holter ECG data will be recorded and transferred from central laboratory. Central laboratory data will be listed separately from local laboratory data.

8 Definitions

8.1 Study day

Study Day 1 is the date of first administration of study drug.

The study day for an event that occurs prior to study Day 1 will be calculated as the date of event minus the date of first administration of study drug.

The study day for an event that occurs on or after study Day 1 will be calculated as the date of event minus the date of first administration of study drug plus one.

8.2 Baseline

For efficacy and safety evaluations (e.g. laboratory assessments and vital signs): the last available pre-dose assessment within 35 days prior to or on Study Day 1 (before the first dose of osilodrostat) is considered as the "baseline" assessment regardless of scheduled/unscheduled assessments.

For ECG assessments, both 12-lead from local and central laboratories as well as 24-hour holder from central laboratory will be collected. Baseline is defined as the average of all ECG measurements taken prior to the dose of study drug from local and central laboratory values separately per subject and type. Post-treatment assessments from local and central laboratories will be reported with corresponding laboratory baseline values.

8.3 Calculating mUFC

To compute the mUFC (mean Urine Free Cortisol) for a patient at any particular visit, at least two UFC specimens are required at that visit. If there are less than two samples available then mUFC will be considered missing for that assessment.

8.4 Study day associated with a Urine Free Cortisol (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.

8.5 Method for calculating confidence interval

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

8.6 Assessment window

Efficacy assessments, e.g. mUFC, morning serum cortisol, steroid hormones, ACTH [redacted], at scheduled visit will be used for summary. If scheduled visit assessments are missing but unscheduled/end of treatment(EoT) visit assessments exist within +/- 3 days from the originally planned visit date (within – 7 days through + 3 days for mUFC only), then those unscheduled/EoT visit assessments may be used for summary. For example, if a subject did not have an assessment at Week 12 but had those at EoT visit within specified time window, then EoT assessments will be used for efficacy summary, even though he may withdrew the study earlier after Week 10.

Summary of safety assessments will be mainly based on scheduled visits only except for shift tables and summary by visit. For summary of safety endpoint by visit, unscheduled/EoT assessment may be used when a scheduled assessment on treatment period is not available and unscheduled/EoT assessment was collected within +/- 3 days from the scheduled visit date. In shift tables, all post-treatment assessments on treatment period will be considered, unless otherwise specified.

9 Changes from planned analysis in the study protocol

The following changes have been made from the analysis planned in the protocol.

Table 9-1 Change from planned analysis

Section	Changes	Rationale
Section 7.2.1 Exposure to study treatment	Summary will be performed for Safety analysis set instead of full analysis set.	In order to see the impact for safety assessment.
Section 7.5.2 Laboratory abnormalities	Summary of Hy's Law criteria is added.	Further data look is required for liver related toxicity and to be consistent with safety guideline.

Section	Changes	Rationale
Section 7.5.2.1 Hematology, chemistry, urinalysis, coagulation and thyroid panel	Frequency table for newly occurring on-treatment grades ¾ is changed to shift table from baseline to worst pots-baseline	In order to be consistent with oncology standard
Section 7.5.3 Vital signs	% change from baseline is removed from the table changed	In order to be consistent with oncology standard
Section 7.5.4 ECG	Shift table is changed to summary of abnormal table	In order to be consistent with oncology standard

10 References

[Nawada H (1999)] Nawada H, Takayanagi R, Nakagawa H, et al (1999). Nationwide epidemiological survey of disorders of adrenal hormones in Japan. Annual report of the Ministry of Health and Welfare "Disorders of adrenal hormones" Research Committee, Japan: 11-55.

[S Webb (2008)] Webb S, Badia X, Barahona M, 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.

11 Appendices

11.1 Appendix 1: Cushing's Syndrome Quality of Life Questionnaire

S Webb et al published scoring and standardization method (S Webb et al. 2008). Each questionnaire of the CushingQOL has a scale of 1-5 where `1` corresponding to `Always` or `Very much` and `5` to `Never` or `Not at all`. The lower the score, the greater the impact on HRQoL. The score is the sum of all the item response and can range from 12 (worst) to 60 points (best).

To simplify interpretation of scores, standardization on a scale from 0 (worst) to 100 (best) can be calculated with the following formula:

$Y=\{[(X) - min]/(max-min)\}x\ 100$

Where Y is the recalculated score, X is the sum of all the item responses within the study score, `min` is the minimum and `max` is the maximum possible score.

11.2 Appendix 2: Imputation rules for partial or missing dates

11.2.1 For exposure data

Partial dates will remain partial in the data listing. For the purpose of analysis, the following imputation rules will be used for exposure data.

If date of last administration is completely missing and there is no EoT CRF page, the subject is considered as on-going and cut-off date should be used as the last dosing date for interim report.

If date of last administration is completely or partially missing and the EoT CRF page is available:

- The date of last administration is completely missing and the EoT visit date is complete, then this latter date should be used.
- Only Year (yyyy) of the dose end date is available and yyyy < the year of EoT date, then use **Dec31yyyy**
- Only Year (yyyy) of the dose end date is available and yyyy = the year of EoT date, then use **EoT date**
- Both Year (yyyy) and Month (mm) are available for the date of last administration and yyyy = year of the EoT date and mm < the month of EoT visit, then use **the last day of the Month (mm)**
- After imputation, compare the imputed date with the start date of that specific record, if the imputed date is < start of that record, then use **the start date of that record.**

Subjects with missing start dates are to be considered missing for all study treatment component related calculations. Therefore, if the date of first administration is missing, then the date of last administration should not be imputed.

11.2.2 For AE and concomitant medication

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

- If year is completely missing, then no imputation will be performed.
- If year (yyyy) < treatment year
    - If month (mm) is missing, then use 01Jul of the year (yyyyy).
    - If month (mm) is known, then use 15th of the month (mm).
- If year (yyyy) = treatment year
    - If month (mm) is missing, then use treatment start date + 1.
    - If month (mm) < treatment month, then use 15th of the month (mm).
    - If month (mm) >= treatment month, then use max of (1st of the month (mm), treatment start day + 1)
- If year (yyyy) > treatment year
    - If month (mm) is missing, then use 1Jan of the year (yyyy).
    - If month (mm) is non-missing, then use max of (1st of the month (mm), treatment start day + 1).