NOVARTIS

Clinical Development

LCI699

CLCI699C2201 / NCT01331239

A proof of concept, open-label, forced titration, multi-center study to access the safety/tolerability and efficacy of 10-weeks treatment of LCI699 followed by a 12-week treatment period in patients with Cushing's disease

RAP Module 3 – Detailed Statistical Methodology

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Version	Date	Changes
Final 1.0	16-Oct-2013	NA
Amendment 2	13-Mar-2019	Updated for the Final CSR analysis The main changes are: Section 1: Addition of further protocol amendment details Section 3: Update of study objectives to align them with the Final CSR Section 5: Update to cutoff date used for Final CSR analyses Section 7.3.2: Secondary efficacy analyses updated Section 7.4: PK evaluations removed for Final CSR Section 7.5.1.3: Addition of text for the AE disclosure outputs Section 7.5.1.4: Removed specific AE summaries to be performed Table 8-2: Addition of extension 2 visits to the visit summary table.

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List of abbreviations

ACTH	Adrenocorticotropic Hormone
AE	Adverse Event
ATC	Anatomic Therapeutic Chemical (Classification)
BMI	Body Mass Index
CI	Confidence Interval
CRF	Case Report/Record Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CTC	Common Terminology Criteria
DBP	Diastolic Blood Pressure
ECG	Electrocardiograms
EOS	End of Study
EOT	End of Treatment
FAS	Full Analysis Set
FPG	Fasting Plasma Glucose
HbA1C	Glycosylated Hemoglobin
HPA (-Axis)	Hypothalamic Pituitary Adrenal
MRI	Magnetic Resonance Imaging
PD	Pharmacodynamics
PoC	Proof of Concept
RAP	Report Analysis Plan
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
UFC	Urinary Free Cortisol
ULN	Upper limit of normal range

1 Introduction

This document describes the detailed statistical methodology to be used in analyzing the data for the Final database lock collected consequent to Amendment 9 to study CLCI699C2201 in patients with Cushing's disease.

The analyses described are predominantly for the core PoC follow-up cohort (defined in Section 6.2) and the expansion cohort (defined in Section 6.3). These analyses will be conducted after all enrolled patients have completed the extension phase or discontinued earlier. Analyses will be reported in the Final CSR.

A history of the protocol amendments is provided below:

Amendment 1, 17-DEC-2010

Amendment 1 amended the inclusion criteria to ensure that only Cushing's Disease patients are enrolled. The definition of a positive response to LCI699 has been revised to include ≥50% decrease in urine free cortisol (UFC) in addition to normalization of UFC. The study stopping rules for the study have also been amended to minimize premature termination of a subject from the study for AEs that are expected in this population or are efficacy related. In addition, the interim analysis for lack of efficacy has been removed to allow collection of more data for adequate evaluation of LCI699 in this small study. To maximize the utilization of all available data, the Last Observation Carried Forward (LOCF) method has been added to impute missing data for the primary endpoint. The opportunity has also been taken to remove minor inconsistencies between the protocol text and Schedule of Assessments as well as the addition of a Saliva log.

Amendment 2, 31-JAN-2011

Amendment 2 updated the blood log with regards to the amount of blood taken. The original optimal testing blood volume estimates received from the central labs were plasma/serum volumes instead of whole blood estimates. Due to the expected yield of plasma/serum from the collected blood, the amount of blood taken has increased from 244 ml to 454 ml per subject. This blood will be collected over a period of approximately 3 months.

Amendment 3, 16-MAR-2011

Amendment 3 revised and clarified the statistical analysis that would occur at the end of the study. In addition, the need for a UFC assessment at screening has also been removed to reduce undue burden to the patients.

Amendment 4, 26-MAR-2012

Amendment 4 amended this proof of concept (PoC) study by enrolling a new cohort (Expansion cohort) of patients and evaluating the long-term efficacy and safety of LCI699 treatment for a total duration of 22 weeks. This longer treatment period will help address questions on the sustainability of the cortisol reductions and longer term safety. At the end of the 22 weeks, patients will have the option to enter into the long term extension for duration up to 12 months.

Amendment 5, 05-MAY-2013

Amendment 5 added intensified ECG monitoring in the study to further enhance patient safety and collect additional safety information. The maximum LCI699 study dose was reduced from 50 mg bid to 30 mg bid to avoid any QTcF prolongation effect. Inclusion and exclusion criteria are modified to exclude patients who have pituitary irradiation within 5 years prior to study entry. Escape analysis is added to summarize patients who lost UFC control after attained normalization on LCI699.

Amendment 6, 14-Apr-2014

The purpose of this protocol amendment is to continue the study to monitor patients for long - term safety and efficacy, and to provide continued access to LCI699 to patients who have completed long term extension-1.
In addition, the protocol has been updated to indicate that the formulation of LCI699 will be changed from capsules to tablets during long term extension-2.

Amendment 7, 17-Feb-2016

The primary purpose of this protocol amendment is to ensure patient safety by adding specific criteria for the identification and management of patients with potential drug induced liver injury (DILI).
Update to the requirement for contraception by male study participants.
Clarification of protocol language regarding withdrawal of consent, study drug discontinuation, and discontinuation procedures

Amendment 8, 11-Jul-2017

The main purpose of this amendment is to provide continued access to the study drug for those patients benefitting from the treatment into a separate long-term safety follow-up study (roll-over study) is set up at participating sites. Based on this, the end of study definition has been updated.

Amendment 9 (03-May-2018)

The purpose of this amendment is to extend the study end date from 31 December 2018 to 31 December 2019 to allow continued access to the study drug for those patients benefitting from the treatment until a separate long-term safety follow-up study (roll-over study) is set up at participating sites.

Additional updates were made to the Protocol glossary and withdrawal of informed consent section to align with the new Personal Data and Withdrawal of Consent language requirement.

2 Study description

This is a proof of concept, open-label, single arm, sequential dose-escalation, multi-center study to assess the safety/tolerability and efficacy of LCI699 in patients with Cushing's disease.

The study will consist of a screening period of up to 60 days (to allow adequate washout period for any medications that modify cortisol levels), a 10-14-day baseline period, a 10-week sequential dose escalation treatment period, a 12-week treatment period at the last efficacious

dose, an End-of-Treatment (EOT)-Core evaluation at the end of 22 weeks, and an optional 12-month extension. Patients are to have an end-of-study (EOS) visit 28 days after the last drug administration.

Following protocol amendment 6, the study was extended (Extension-2) to provide continued access to LCI699 to patients who have completed long term extension-1.

Patients who enrolled into the study prior to Amendment 4 and completed the trial treatment will be allowed to re-enter the study as the core PoC follow-up cohort if their Urinary Free Cortisol (UFC) is > upper limit of normal range (ULN) and all other eligibility criteria have been met. In addition, approximately 15 new patients with Cushing's disease who did not previously participate the study will be enrolled and comprise the expansion cohort. Patients from both the core POC follow up cohort and the expansion cohort will be screened and follow similar visit schedule for this 22-week treatment period except certain differences described in the protocol.

Every 7 days during the baseline period, patients will collect a morning and evening saliva sample, and will also perform at least three 24 hour urine collections. Patients will bring urine bottle on Day -3, at which time the baseline safety and Pharmacodynamics (PD) samples will be collected. All baseline evaluation result will be reviewed, and confirmation of inclusion/exclusion criteria determined prior to the patient dosing with LCI699.

Newly enrolled patients (the expansion cohort) with a baseline 1.5xULN< UFC ≤ 3xULN will start at 2 mg bid on Day 1. Patients with baseline UFC > 3xULN will start LCI699 at 5 mg bid on Day 1. Every 7 days during the dose escalation period, patients will collect a morning and evening saliva sample. Patients will perform three 24 hour urine collections within 7 days of Day 7±1 and 14±1 day. A pre-dose PK sample and post-dose PK samples at 1, 1.5, 2, 4, and 6 hours post morning dose will be collected. The schedule of events will continue every 2 weeks for the dose escalation period, with the dose of LCI699 increasing as represented in Figure 2-1. If at any time the patient's UFC is < ULN, dose escalation will be halted and the patient will remain on the current efficacious dose through Week 10, with continued monitoring of UFC response every 2 weeks to allow for continued dose adjustments. If at any time the patient experiences side effects which are either intolerable or meet dose adjustment criteria, the prescribed dose will be adjusted as outlined in Section 6.7.3 in study protocol.

Patients in the core PoC follow-up cohort will be started at the penultimate LCI699 dose that was efficacious and well tolerated during the core PoC study with the possibility to up-titrate the dose within one week based on the tolerability.

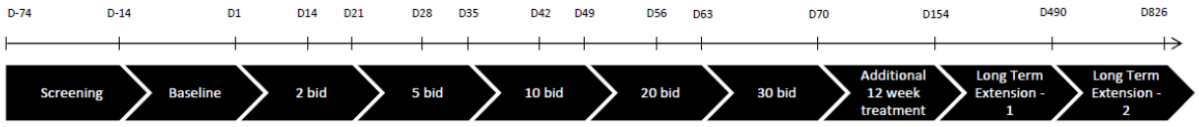
Safety assessments will include physical examinations, electrocardiograms (ECGs), vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, urinalysis,) adverse events (AEs), and serious adverse events (SAEs) monitoring.

At Day 70 ± 2 days (Week 10), all patients will enter the 12 week assessment period. Three visits will be performed at Day 98, Day 126, and Day 154. Patients will continue the home saliva collections every 7 days twice daily, and perform three 24 hour urine collections over 7 days prior to the next scheduled visit. From Day 70 through Day 154, patients can have their LCI699 dose adjusted based on the criteria in Section 5.5.4 in the study protocol. At Day 154, patients will complete the End-of-Treatment-Core visit. They have the option to enter the 12-month extension phase at the investigators discretion provided they do not meet any discontinuation criteria. During the optional long term extension, patients will visit monthly for

the first 6 months and every 3 months from month 6 through month 12. Patients not continuing into the optional long term extension will also complete an End-of-Study visit 28 days after the last dose administration.

The study design for newly enrolled patients (the expansion cohort) is depicted in Figure 2-1 below. Patients that were in the core POC study and re-enrolled (core POC follow up cohort) will have LCI699 dosing as described in the text above.

Figure 2-1 Study Design



Note: patients with baseline UFC > 3×ULN will start at 5 mg bid (in lieu of 2 mg bid) at Day 1.

3 Objectives

The primary objective of this study as well as several other objectives related to the safety and efficacy of 10-week and 22-week treatment of LCI699 have already been analyzed for the PoC cohort and described previous CSRs. For the sake of completeness, the objectives of the protocol (up to and including Amendment 9) are listed below.

The Final CSR will concentrate on reporting long-term safety and efficacy of osilodrostat in patients with Cushing's disease, [redacted]. For the assessment of efficacy, the analyses given for the secondary objectives will form the basis of the assessments. For each objective listed below it is indicated if this will be included in the Final CSR analyses.

3.1 Primary objective

- To assess the effect of 10-week treatment of LCI699 on 24 hour urine free cortisol (UFC) in patients with Cushing's disease; not included in Final CSR

3.2 Secondary objectives

- To assess the 10-week safety and tolerability of multiple doses of LCI699 in patients with Cushing's disease; not specifically included in the Final CSR
- To assess the 22-week safety and tolerability of multiple doses of LCI699 in patients with Cushing's disease; extended to cover entire study duration, and included in the Final CSR
- To assess the effect of 22-week treatment with LCI699 monotherapy on 24 hour urine free cortisol (UFC) in patients with Cushing's disease; extended to cover entire study duration, and included in the Final CSR

  At each scheduled assessment, the proportion of responders (mUFC $\leq$ ULN or $\geq$ 50% decrease from baseline) will be presented.

  In addition, the proportion of patients classified as either controlled or partially controlled will be determined as follows:

  - Controlled UFC: defined as a mean of UFC level $\leq$ ULN
  - Partially controlled UFC: defined as a mean of UFC level > ULN but with $\geq$ 50% reduction from baseline
- To assess the effect of LCI699 on steroid hormones of Hypothalamic Pituitary Adrenal (HPA)-axis in plasma, urine and saliva; included in the Final CSR
- To assess the effects of LCI699 on improving the metabolic abnormalities (hypertension, dyslipidaemia, obesity, insulin sensitivity, glycosylated hemoglobin (HbA1c) and fasting plasma glucose (FPG)) of Cushing's disease; included in the Final CSR
- To assess the steady state pharmacokinetics of LCI699 in patients with Cushing's disease; not included in the Final CSR
- To assess escape. Escape is defined as loss of UFC control (i.e. UFC > ULN) on at least 2 consecutive visits at the highest tolerated dose after previously attaining UFC normalization; included in the Final CSR

4 Sample size and power considerations

The 15 patients in the expansion cohort will afford the level of precision around the estimate of the responder rate (controlled or partially controlled as defined in the secondary objective) at Week 22, as shown in Table 4-1.

Table 4-1 Precision level (two-sided 95% confidence interval for each response rate) in the study

# Patients / #Responders	Response rate and two-sided 95% CI in (%)			
	N=12	**N=13**	**N=14**	**N=15**
0	0 (0, 26)	0 (0, 25)	0 (0, 23)	0 (0, 22)
1	8 (0.2, 38)	8 (0.2, 36)	7 (0.2, 34)	7 (0.2, 32)
2	17 (2, 48)	15 (2, 45)	14 (0.2, 43)	13 (2, 40)
3	25 (5, 57)	23 (5, 54)	21 (5, 51)	20 (4, 48)
4	33 (10, 65)	31 (9, 61)	29 (8, 58)	27 (8, 55)
5	42 (15, 72)	38 (14, 68)	36 (13, 65)	33 (12, 62)
6	50 (21, 79)	46 (19, 75)	43 (18, 71)	40 (16, 68)
7	58 (28, 85)	54 (25, 81)	50 (23, 77)	47 (21, 73)
8	67 (35, 90)	62 (32, 86)	57 (29, 82)	53 (27, 79)
9	75 (43, 95)	69 (39, 91)	64 (35, 87)	60 (32, 84)
10	83 (52, 98)	77 (46, 95)	71 (42, 92)	67 (38, 88)
11	92 (62, 100)	85 (55, 98)	79 (49, 95)	73 (45, 92)
12	100 (74, 100)	92 (64, 100)	86 (57, 98)	80 (52, 96)
13		100 (75, 100)	93 (66, 100)	87 (60, 98)
14			100 (77, 100)	93 (68, 100)
15				100 (78, 100)

5 Data Cutoff for Analyses

The data cutoff for the Final CSR will be the date on which the last patient either completes extension-2, or discontinues from the study.

6 Analysis Populations

The 12 Cushing's disease patients who were enrolled in the study prior to protocol Amendment 4 comprise the core PoC cohort. Patients who are re-enrolled into the study after protocol Amendment 4 comprise the core PoC follow-up cohort. The 15 new patients enrolled after protocol Amendment 4 comprise the expansion cohort. In the Final CSR, the two cohorts will be presented separately for efficacy and safety analysis, alongside an All Patients column which will combine the patients from the two cohorts.

6.1 Core PoC follow-up cohort:

Full analysis set (FAS): all patients in Core PoC follow-up cohort.

Safety analysis set (SAS): all patients in the Core PoC follow-up cohort who received at least one dose of study drug after reentering the study.

6.2 Expansion cohort:

Full analysis set (FAS): all patients in the Expansion cohort.

Safety analysis set (SAS): consists of all patients in the Expansion cohort who received at least one dose of study drug after protocol Amendment 4.

The analysis sets to be used for various analyses in each cohort are summarized in the following table:

Table 6-1 Analysis sets

	FAS	SAS
Patient Disposition	√	
Protocol Deviation	√	
Demography and baseline disease characteristics		√
Medical History		√
Prior Medication		√
Concomitant Medications		√
Exposure to study medication		√
Primary efficacy analyses		√
Other efficacy analyses		√
Safety analyses		√
PK analyses		
PK/PD analyses		

6.3 Imputation rules of partial or missing dates

Partial dates will remain partial in the data listing. For the purpose of analysis, the following imputation rules will be used to impute the partial dates: if the day and month is missing, it will be replaced by 30th June (to be used only for prior events, e.g. medical history); if only the day is missing it will be replaced by the 15th of that month. For the dates known to be within the trial period, if this imputation make the date later then the trial completion date, use the trial completion date; if the imputed date is earlier then the first medication date, use the first medication date.

The imputation of partial date for AE and concomitant medication will follow Novartis standard rules (See module 8 for details).

7 Statistical analyses

7.1 Patients studied

7.1.1 Grouping for analyses

For analyses of all endpoints, patients will be grouped into expansion cohort and core PoC follow-up cohort, respectively (defined in Section 6). Additionally, for the Final CSR, an All Patients column will be included for all relevant analyses.

7.1.2 Patient Disposition

Patient disposition will be summarized separately using the FAS. Counts of the following items will be included in disposition summaries..

- Patients enrolled:
    - Not treated
    - Treated
- Patients treated
    - Discontinued
- Primary reason for end of treatment in the core phase (prior to Week 22)
- Patients completed core phase
    - Patients did not enter extension phase
    - Entered extension phase
        - Completed extension phase
        - Discontinued in extension, with reasons for discontinuation

7.1.3 Demography and baseline disease characteristics

Summary statistics will be provided for demographics, and baseline characteristics using safety analysis set for each cohort. Categorical data will be presented by frequencies and percentages. Continuous data will be summarized by mean, standard deviation, minimum, median, and maximum. All data for background and demographic variables, as well as medical history, current medical conditions, results of lab screens, and any other relevant information will also be presented in listing.

7.1.4 Medical history

Relevant medical history and ongoing medical conditions will be summarized and listed. The summary will be presented for SAS by primary system organ class (SOC) and preferred term (PT).

7.1.5 Prior therapy

Medications taken prior to first dose of LCI699 will be listed and summarized for SAS by ATC class and preferred term by means of frequency counts and percentages.

7.1.6 Protocol deviations (PDs)

Protocol deviation criteria are specified in the Validation and Planning (VAP) document Module 3. The number and percentage of FAS patients with protocol deviations will be provided for PDs by Week 22, and by the end of extension phase.

All protocol deviations up to data cutoff will be listed.

7.2 Study medication

7.2.1 Exposure to Study Treatment

The duration of exposure to the study drug will be summarized by descriptive statistics using the SAS.

Duration of exposure is calculated as

Duration of exposure (weeks) = (min (date of last administration of LCI699, date of data cut-off) – date of first administration of LCI699 + 1)/7

7.2.2 Concomitant medication

Concomitant medications will be summarized and listed by Anatomical Therapeutic Chemical (ATC) class and preferred term by means of frequency counts and percentages.

7.3 Efficacy evaluation

7.3.1 Primary efficacy analysis

7.3.1.1 Week 10 treatment effect

As mentioned in Section 3, the primary efficacy analysis has already been reported in a CSR. It was based on the core PoC cohort. The 10-week treatment effect of LCI699 in the core PoC follow-up cohort and expansion cohort will be analyzed as part of the secondary efficacy analyses (described below) and reported in a separate CSR.

7.3.2 Secondary efficacy analysis

7.3.2.1 Week 22 treatment effect

As mentioned in Section 3, the Week 22 treatment effect of LCI699 has already been reported in a CSR.

Similar analyses to those performed for the Week 22 treatment effect will be performed for scheduled assessment time points during the extension periods of the study.

A patient is considered to be a responder at a particular time point if the mean UFC level (at least two 24-hour measurements) at that time point is ≤ ULN or represents a ≥ 50% decrease from baseline. Patients who discontinue for a disease or treatment related reason (e.g. death, adverse event, clinical disease progression etc.), or whose mean UFC levels are higher than the normal limit and experience < 50% decrease in UFC are classified as non-responders or uncontrolled. If mUFC is missing at a particular time point, then the value will not be imputed but the patient will be considered a non-responder at that time point.

The denominator for the response rate calculation is the number of patients in the safety analysis set for weeks 10 and 22, which is the core phase. For time points after the core phase, the denominator will exclude patients who did not enter the extension phase. Patients who discontinued due to administrative reasons will also not be included in the denominator of any time points after the time of their discontinuation. In addition, patients who are ongoing without reaching the analysis time point will also be excluded. Early discontinued patients (including those discontinuing in the core phase) will be considered as non-responders for all time points after discontinuation.

As a supportive analysis, the response rate will be calculated using only the number of observed mUFC samples at each time point. Patients who have discontinued prior to the assessment time

point, or who are ongoing but do not have a valid mUFC value, will not be counted in the denominator.

The proportion of responders and the associated two-sided 95% confidence interval will be estimated using the exact method.

In addition, responders will be classified further into controlled and partially controlled. Controlled UFC responder is defined as the patient whose mean UFC ≤ 1.0 × ULN. Partially controlled UFC responder is defined as the patient whose mean UFC > 1.0 × ULN but declined by at least 50% from baseline. The proportion of patients with controlled or partially controlled will be provided.

7.3.2.2 Treatment effect on steroid hormones of HPA-axis

Descriptive statistics will be generated for the change from the respective baselines to different time points in mUFC, plasma adrenocorticotropic hormone (ACTH), serum cortisol, and steroid hormones, plasma 11-deoxycortisol, 11-deoxycorticosterone, salivary cortisol and aldosterone (morning and evening), urine creatinine, plasma and urine sodium, plasma and urine potassium, plasma renin, testosterone, estradiol, insulin, LH, FSH, IGF-1, free T4, TSH, two-sided 95% CIs using exact method will be provided for the changes from baseline.

7.3.2.3 Treatment effect on metabolic abnormalities

The treatment effect on improving the metabolic abnormalities including hypertension, dyslipidaemia, obesity, insulin sensitivity, HbA1c and FPG will be assessed by descriptive statistics on the change from baseline in systolic blood pressure (SBP), diastolic blood pressure (DBP), weight, body mass index (BMI), lipids which includes total cholesterol, triglycerides, HDL-cholesterol, and LDL-cholesterol, QUICKI, HbA1C, and FPG over time, as well as their two-sided 95% CIs using exact method, where QUICKI is the quantitative insulin sensitivity check index derived using the inverse of the sum of logarithms (base 10) of the fasting insulin and fasting glucose as in the following formula:

1/(log(fasting insulin μU/mL)+log(fasting glucose mg/dL))
In addition, a listing of relevant concomitant medication(s), with total daily doses and the corresponding cardiovascular/metabolic variable (blood pressure, fasting glucose, HbA1c, fasting lipid profile) lab over time as well as figures and statistical modeling may be provided as an exploratory analysis.

7.3.2.4 Escape analysis

Only patient who attained UFC normalization during the study will be included in this analysis, where escape is defined as the loss of UFC control (i.e. UFC > ULN) on at least 2 consecutive visits at the highest tolerated dose after previously attaining UFC normalization. “First-time escape” is used to describe the first occurrence of 2 consecutive visits with uncontrolled UFC at the patient’s highest tolerated dose after attaining UFC normalization. Time to escape is defined as the number of weeks from the visit of first UFC normalization (mUFC <= 1x ULN) to the first visit of first-time escape. The definition for “highest tolerable dose” of LCI699 is provided in this paragraph. For patients who have no safety issue, 30 mg bid is the highest

tolerated dose. For patients who have dose reduction(s) because of an intolerable adverse event, the highest tolerated dose is the highest dose at which no AE requiring dose reduction is reported. For patients who discontinue the study due to AE, the highest tolerated dose is the highest prior dose at which no intolerable AE was reported. For all other situations (i.e., LCI699 dose is < 30mg bid, and there has been no AE leading to dose reduction or study drug discontinuation reported at the effective treatment dose), patients will be considered as not reaching their highest tolerated dose.

The median time to escape and corresponding two-sided 95% confidence interval will be calculated using Kaplan-Meier methodology for each cohort. The Kaplan-Meier curves will be presented. In this analysis, a patient who never had two consecutive visits with uncontrolled UFC at his/her highest tolerated dose will be censored at his/her last visit with mUFC assessment. In addition, time to escape will be summarized using descriptive statistics by cohort for patients who meet escape criteria.

7.4 Pharmacokinetic evaluation

No pharmacokinetic assessments were performed after Week 22, and the pharmacokinetic results have been reported in previous CSRS. No PK analyses will be included in the Final CSR.

7.4.3 Other biomarkers

Not applicable.

7.5 Safety evaluation

The assessment of safety will be based on the frequency of adverse events, laboratory values that fall outside the pre-determined ranges, vital signs, as well as ECG data.

7.5.1 Adverse events (AEs)

All information obtained on adverse events will be displayed by patient.

The number and percentage of subjects with adverse events will be tabulated by system organ class and preferred term. A subject with multiple adverse events within a body system is only counted once towards the total of this body system if no change in severity.

7.5.1.1 Coding of AEs

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

7.5.1.2 Grading of AEs

AEs will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (http://ctep.cancer.gov/forms/CTCAEv4.pdf).

The CTCAE represents a comprehensive grading system for reporting acute and late effects of cancer treatments. CTCAE v4.0 is graded by definition 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. Information regarding death will be collected in the "Study Phase Completion Evaluation" CRF pages.

7.5.1.3 General rules 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) and ending no later than 28 days after last study treatment or the follow-up visit, whichever is later. 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.

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. A subject with multiple occurrences of an AE will be counted only once in the AE category. Separate AE summaries will be presented by primary system organ class, preferred term, and maximum CTC grade. A patient with multiple CTC grades for an AE will be summarized under the maximum CTC grade recorded for the event. In the summaries presented by grade, all AEs will be pooled regardless of whether they are CTC gradable or not. 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.
For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on on-treatment adverse events which are not serious adverse events with an incidence greater than 5% and 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 set population.

If for the 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 of study treatment relationship will be provided by SOC and PT.

7.5.1.4 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.

7.5.2 Laboratory abnormalities

For analyzing laboratory results, data from all sources (central and local laboratories) will be combined. The summaries will include all laboratory assessments up to data cut-off date. All laboratory assessments will be listed. Results will be reported for each visit at which collected in the core, follow-up, and extension phases through the last study visit.

Biochemistry, hematology, and urine laboratory data, will be presented using

- shift tables using CTC grades (if available), otherwise by normal ranges: both standards from baseline to most extreme post-baseline value and baseline to last value
- listings flagging values with elevated CTC grades (i.e. greater than 0), and outside of the normal ranges otherwise

All laboratory values will be converted into SI units and the severity grade derived using NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Blood glucose will be presented as mg/dL and will be assessed using the ADA criteria 2010. Insulin and QUICKI may also be presented in US unit. 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.

The following summaries will be produced for the laboratory data (by laboratory parameter):

- Number and percentage of patients with worst post-baseline CTC grade (regardless of the baseline status). Each patient will be counted only for the worst grade observed post-baseline
- 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
- Shift tables using CTC grades to compare baseline to the worst post-baseline values will be produced for hematology and biochemistry laboratory parameters with CTC grades
- For laboratory parameters in which CTC grades are not defined, shift tables to the worst post-baseline values will be produced using the low/normal/high classifications based on laboratory reference ranges
- Selected laboratory data will be also be displayed by presenting summary statistics of change from baseline values.

The following listings will be produced for the laboratory data:

- Listing of all laboratory data with values flagged to show the corresponding CTC grades and/or ADA classifications (normal/impaired/diabetic) and the classifications relative to the laboratory reference ranges
- Listing of notable laboratory abnormalities (i.e. newly occurring CTC grade 3 or 4 laboratory toxicities).

7.5.3 Vital signs

All vital signs data (height (cm), weight (kg), body temperature (^{0}C), sitting pulse rate (bpm), systolic/diastolic blood pressure (mmHg)) will be listed by patient and visit/time, and abnormalities will be flagged on listing. Shift table based on notable value will be provided for vital signs. For blood pressure, we will provide the mean of the 3 measurements.

The criteria for clinically notable abnormalities are defined as follows:

7.5.3.1 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

7.5.3.2 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

7.5.4 ECG

Bazett's formula (QTcB) and Fridericia's formula (QTcF) will be used to calculate the heart rate-corrected QT interval (msec) on the heart rate (HR bpm) and QT (msec) as follows.

QTcB (msec) = QT / $(RR)^{1/2}$ and QTcF (msec) = QT / $(RR)^{1/3}$All ECG data (heart rate (bpm), PR interval (msec), QT interval (msec), QRS duration (msec), QTcB interval (msec)) will be listed by patient and visit/time. Abnormalities will be flagged.

Summary statistics (n, mean, standard deviation, minimum, median, and maximum) will be provided by visit/time for the above parameters. Descriptive statistics will be provided for change from baseline to different time points in heart rate, PR interval, QT interval, QRS duration, and QTcB interval. Shift table based on notable values will be provided for ECGs.

The notable criteria for PR is

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

The notable criteria for QRS is

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

The notable criteria for HR are

- Increase > 25% compared to baseline to a post-baseline value > 100 bpm
- Decrease > 25% compared to baseline to a post-baseline value < 50 bpm

The notable criteria for QT, QTcF, and QTcB are

- an increase from baseline > 30 ms at any post-baseline
- an increase from baseline > 60 ms at any post-baseline

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 (date of event – 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 (date of event – date of first administration of study drug) + 1.

8.2 Baseline

For efficacy and safety evaluations, the last available pre-dose assessment within 20 days prior to study Day 1 is taken as “baseline” assessment. For MRI and ECG, the last available pre-dose evaluation prior to study Day 1 will be taken as “baseline” assessment. If several measurements are taken on the same day, the last one prior dose is used as measurement of that day.

8.3 Visit number

The time point (Day/Week) associated with an assessment, will be determined by the visit number assigned to the corresponding assessment in the database. The mappings of visit numbers to time points in the core study and the extension study are provided in the table below. Saliva samples as well as other ECG, lab and PK parameters collected not following protocol schedule may only be presented in listings and not included in any statistical analysis.

Table 8-1 Visit number in core phase

Core study Visit	Day/Week	Clarifying Notes
Visit 1	Day -74 to Day -15	Screening
Visit 2	Day -14 to Day -1	Baseline
Visit 3	Day 1	Dose escalation / Treatment period
Visit 4	Day 7/Week 1	Dose escalation / Treatment period
Visit 5	Day 14/Week 2	Dose escalation / Treatment period
Visit 6	Day 28/Week 4	Dose escalation / Treatment period
Visit 7	Day 42/Week 6	Dose escalation / Treatment period
Visit 8	Day 56/Week 8	Dose escalation / Treatment period
Visit 9	Day 70/Week 10	Dose escalation / Treatment period
Visit 10	Day 98/Week 14	12-week Treatment period
Visit 11	Day 126/Week 18	12-week Treatment period
Visit 775	Day 154/Week 22	End of treatment in core phase
Visit 778	28 days after last dose	End of study

Table 8-2 Visit number in extension phase

Extension study Visit	Day/Week	Clarifying Notes
Visit 12	Day 154/Week 22	Long term extension 1
Visit 13	Day 182/Week 26	Long term extension 1
Visit 14	Day 210/Week 30	Long term extension 1
Visit 15	Day 238/Week 34	Long term extension 1
Visit 16	Day 266/Week 38	Long term extension 1
Visit 17	Day 294/Week 42	Long term extension 1
Visit 18	Day 322/Week 46	Long term extension 1
Visit 19	Day 406/Week 58	Long term extension 1
Visit 776	Day 490/Week 70/ End of Treatment Ext 1	End of treatment in extension phase 1
Visit 20	Month 16	Long term extension 2
Visit 21	Month 19	Long term extension 2

Extension study Visit	Day/Week	Clarifying Notes
Visit 22	Month 22	Long term extension 2
Visit 23	Month 25	Long term extension 2
Visit 24	Month 28	Long term extension 2
Visit 25	Month 31	Long term extension 2
Visit 26	Month 34	Long term extension 2
Visit 27	Month 40	Long term extension 2
Visit ...	Month ...	Long term extension 2
Visit 777	End of Treatment Ext 2	End of treatment in extension phase 2
Visit 778	28 days after last dose	End of study

After Visit 27 / Month 40, visits occur every 6 months. The Visit Number increases by 1 each time, and the Month increases by 6.

Unlike the above visits that are scheduled to occur after a fixed number of days have elapsed since Day 1, the Visits 777 (End-of-Treatment in core phase and extension phase) and 778 (End of study) are scheduled when the patient either completes the respective study phase or decides (or is mandated by the protocol) to prematurely discontinue from the study.

If such a visit happens neither too soon nor too late after the actual last scheduled visit, then it will be mapped to the next scheduled visit that would have occurred had the patient continued in the study. Otherwise, the early discontinuation visit will be mapped to an unscheduled visit.

The 777visit will be considered to have occurred neither too soon nor too late after the actual last scheduled visit if number of days between the two visits is

i. at least half of the planned gap between the patient's actual last scheduled visit and the next scheduled visit and
ii. at most the total of
    a. the planned gap between the patient's actual last scheduled visit and the next scheduled visit (that would have occurred if the patient had not discontinued)
    b. half of the planned gap between the patient's next two scheduled visits (that would have occurred if the patient had not discontinued).

If the number of days between the 777visit and last scheduled visit (last scheduled visit +1) is less than the range specified above, then the 777visit will be mapped to an unscheduled visit of the last scheduled visit (last scheduled visit +1); if it's more than the range, then it will be mapped to an unscheduled visit of the last scheduled visit + 1 (last scheduled visit+2).

For example, if a patient's last scheduled visit is Visit 6, then his next two planned visits would have been Visit 7 and Visit 8 if he had not discontinued. Thus, the early discontinuation visit will be mapped to Visit 7 only if it occurs between 7 (Day 42 – Day 28)/2 and 21 (14 + (Day 56 – Day 42)/2) days after Visit 6.

Further, if a patient continued into the extension phase, then we set Visit 777 in the core phase to Visit 12 without checking the days-in-between. Visit 778 will not be mapped.

8.4 Calculating mean UFC

Three 24-hour urine specimens will be collected to calculate mean UFC for baseline record and throughout the core study phase. During the long term extension phase, patients will collect two 24-hour urine specimens for calculation of the mean UFC level.

To compute the mean UFC 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 mean UFC will be considered missing for that assessment.

8.5 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 for that visit.

8.6 Conversion of duration in days to duration in months/years

Duration in months = 12 * (Duration in days)/365.25

Duration in years = (Duration in days)/365.25

8.7 Method for calculating confidence interval

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

Two-sided 95% confidence intervals for change and percentage change from baseline will assume normally distributed data and will be calculated using the t-distribution.

9 References

10 Appendix:

Table 10-1 Precision level (two-sided 95% confidence interval for each response rate) in the study

# Patients / #Responders	Response rate and two-sided 95% CI in (%)			
	N=6	**N=8**	**N=10**	**N=12**
0	0 (0, 45.9)	0 (0, 36.9)	0 (0, 30.9)	0 (0, 26)
1	16.7 (0.4, 64.0)	12.5 (0.3, 52.6)	10 (0.2, 44.5)	8 (0.2, 38)
2	33.3 (4.3, 77.8)	25 (3.2, 65.1)	20 (2.5, 55.6)	17 (2, 48)
3	50.0 (11.8, 88.2)	37.5 (8.5, 75.5)	30 (6.7, 65.3)	25 (5, 57)
4	66.7 (22.3, 95.7)	50 (15.7, 84.3)	40 (12.2, 73.8)	33 (10, 65)
5	83.3 (35.9, 99.6)	62.5 (24.5, 91.5)	50 (18.7, 81.3)	42 (15, 72)
6	100 (54.1, 100)	75 (34.9, 96.8)	60 (26.2, 87.8)	50 (21, 79)
7		87.5 (47.4, 99.7)	70 (34.8, 93.3)	58 (28, 85)
8		100 (63.1, 100)	80 (44.4, 97.5)	67 (35, 90)
9			90 (55.5, 99.8)	75 (43, 95)
10			100 (69.1, 100)	83 (52, 98)
11				92 (62, 100)
12				100 (74, 100)