NOVARTIS

LCI699 (osilodrostat)

CLCI699C2301 / NCT02180217

# A Phase III, multi-center, double-blind, randomized withdrawal study of LCI699 following a 24 week, single-arm, open-label dose titration and treatment period to evaluate the safety and efficacy of LCI699 for the treatment of patients with Cushing's disease

Statistical Analysis Plan (SAP) for Final CSR

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| 02-Dec-2019 | Prior to Final DBL | Creation of SAP for Final DBL | Creation of SAP for Final DBL | |

## Table of contents

## List of abbreviations

| | |
|---|---|
| ACTH | Adrenocorticotropic Hormone |
| AE | Adverse Event |
| AESI | Adverse event of special interest |
| ALP | Alkaline Phosphatase |
| ALT | Alanine aminotransferase/glutamic pyruvic transaminase/GPT |
| AST | Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT |
| ATC | Anatomical Therapeutic Chemical |
| BDI-II | Beck Depression Inventory-II |
| BMI | Body Mass Index |
| CI | Confidence Interval |
| CRF | Case Report/Record Form |
| CRO | Contract Research Organization |
| CSR | Clinical Study Report |
| CTC | Common Terminology Criteria |
| DBL | Database lock |
| DBP | Diastolic Blood Pressure |
| DRL | Drug Reference Listing |
| DXA | Dual-energy X-ray absorptiometry |
| 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 |
| LLOQ | The limit of quantitation |
| MedDRA | Medical Dictionary for Drug Regulatory Affairs |
| MID | Minimal Important Difference |
| MRI | Magnetic Resonance Imaging |
| PoC | Proof of Concept |
| PPFAS | Per-Protocol Set for Full Analysis Set |
| PPRAS | Per-Protocol Set for Randomized Analysis Set |
| PRO | Patient-reported Outcomes |
| QoL | Quality of Life |
| QTcF | QT corrected (Fridericia QT formula) |
| RAS | Randomized Analysis Set |
| RMP | Risk Management Plans |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SAS | Safety Analysis Set |
| SBP | Systolic Blood Pressure |
| SCS | Summary of Clinical Safety |

| | |
|---|---|
| SOC | System Organ Class |
| TBIL | Total bilirubin |
| UFC | Urinary Free Cortisol |
| ULN | Upper limit of normal range |
| WHO | World Health Organization |

# 1 Introduction

The SAP document describes the planned statistical analyses for the Final CSR of study LCI699C2301 in the treatment of Cushing's disease. It incorporates analysis of the long-term safety and efficacy of the study, including data collected during both the core phase (up to Week 48) and the optional extension period. The optional extension period will end 16 months after all patients have completed Week 72 or discontinued early (prior to Week 72).

The analysis will be performed after all patients have completed the extension period or discontinued earlier.

The analysis of the core phase, including the results of the primary and key secondary outcomes was detailed in the CSR written following the DBL which occurred once all patients had completed the core phase or discontinued earlier. These details of these analyses can be found in the corresponding SAP, with cover date 06-Jul-2018.

After the interim CSR was published, additional protocol deviations were reported which affect the per-protocol populations used to perform the per-protocol analyses of the primary and key-secondary endpoints, therefore the Final CSR will report the updated results of these per-protocol analyses.

## 1.1 Protocol amendments

At the time of finalization of this document the original study protocol had undergone five amendments, as summarized below.

### Amendment 1, 15-JUL-2014

The purpose of this protocol amendment is to address requests from the Voluntary Harmonization Procedure (VHP) review. Changes made to the protocol during this amendment were summarized below:

- The definition of the optional extension period was revised to specify the length of study treatment.
- The definition of time-to-escape (one of the secondary objectives) was clarified.
- To ensure that pregnancy was identified as an absolute withdrawal criterion, it was moved from the list of general study withdrawal criteria to the list of study specific criteria that require study treatment discontinuation.
- To harmonize with ICH guidelines, treatment discontinuation criteria was revised to include an increase in QTcF > 60 msec from pre-first dose baseline measurement.
- To improve monitoring for potential QT prolongation, 24-hour Holter recordings were added during the extension at Weeks 72 and 96. As a result of this addition, both the Visit Evaluation Schedule and the ECG Collection Table were also revised.

### Amendment 2, 11-Mar-2015

The primary reason for this amendment is to add a local, country-specific intensive PK sampling for China in order to investigate potential ethnic differences in LCI699 pharmacokinetics at steady-state and at doses used in the treatment of patients with Cushing's disease.

Additional changes applicable to all countries include:

- Inclusion of recent LCI699 clinical trial results information (longer-term safety and efficacy data (LCI699C2201) and results of the clinical drug-drug interaction study (LCI699C2102).
- Relaxation of the protocol guidance on narrow therapeutic index/sensitive substrates of CYP1A2, CYP2C19, CYP2D6 and CYP3A4/5 as concomitant medication (based on the results of the clinical drug-drug interaction study (LCI699C2102)).
- Blinding: The pharmacist, the bioanalyst and the pharmacokineticist are also blinded.
- Inclusion criteria:
    - Minimum period since last stereotactic radiosurgery decreased from 3 to 2 years.
    - Rescreening is introduced, some therapies needed washouts are removed and the screening period is extended to accommodate for the need for long washout periods.
- Exclusion criteria:
    - QTcF exclusion limits tightened from >470 ms to >450 ms (males) and >460 ms (females).
    - Definition of post-menopausal status and woman not of childbearing potential is added.
    - Male contraception is no longer required in patients treated with LCI699 based on a thorough review of the mechanism of action of LCI699 and re-evaluation of pre-clinical and clinical data.
    - The criterion on optic chiasm compression is updated and broaden.
    - Euthyroid status is based on investigator's judgment (rather than biochemically).

- [redacted]
- Changes to safety monitoring schedule (removal of non-required assessments timepoints, additional sex hormone assessments, assessment of waist circumference)
- Collection of additional baseline information (such as information on most recent prior medical therapy).
- Permitted concomitant medications now includes spironolactone, eplerenone, cyproterone acetate or finasteride under certain conditions.
- Discontinuation criteria revised to distinguish "confirmed" laboratory abnormalities and "confirmed and persistent laboratory abnormalities"; with the hypokalemia parameter relaxed.
- Central reading of photographs removed, as it is not essential for the study.
- Additional sex hormone assessments (Androstenedione, DHEA and Estrone) are introduced to better characterize the effects on hormone balance.
- The CTCAE version is updated from 4.0 to 4.03.

- The "potential risk" for QT prolongation is changed to "risk", based on one reported SAE with QTcF prolongation in a clinical study evaluating the longer-term efficacy and safety of LCI699 (LCI699C2201).
- The QT monitoring section is clarified and the trigger for doing a triplicate ECG is updated from > 500 msec to > 480 msec.
- Novartis Discontinuation of Clinical Trial Protocol Elements language has been implemented throughout the protocol.

In addition, editorial changes and clarifications were made throughout the protocol.

As of 02 March 2015, 16 patients have provided written informed consent for the study and 10 patients have received LCI699.

### Amendment 3, 29-Mar-2016

The purpose of this amendment is to include the following changes to reduce the risk of dosing errors.

- Expand the description of the dose dispensation process; in particular to emphasize that more than one tablet strength of study drug may be dispensed at the same visit.
- Elaborate on dose adjustments and communication of dosing instructions
- Recommend the use of patient dose instruction card and phone contacts between scheduled visits.

This amendment also includes changes to ensure patient safety by adding specific criteria for the identification and management of patients with potential drug-induced liver injury (DILI). Although there are no known cases of suspected DILI in patients treated with LCI699 to date, these criteria are added in the event that a case of suspected DILI arises in the future.

Other protocol changes are:

- To provide more information regarding the study drug:
  - A summary of the benefit-risk assessment of LCI699 for this trial has been added
  - The results of the thorough QT/QTc study (LCI699C2105) of LCI699 in healthy volunteers has been added
- Additional measurements of serum cortisol and plasma ACTH have been added for patients in China undergoing extensive PK, [redacted].
- Exclusion criterion # 16 is modified to exclude patients with serum total bilirubin > 1.5 x ULN; this is one of the criteria needed for effective screening of patients for potential DILI

The duration of the optional extension period is increased in order to collect additional long-term safety data as well as to provide continued access to the study drug for those patients benefitting from the treatment. Patients can continue on extension period until the last patient completes the core phase or discontinued early from core phase. Patients who continue to benefit from treatment will be offered participation in a separate long-term safety follow-up study. Study CLCI699C2301 ends when seamless transition to the long-term safety follow-up

study is possible or alternative treatment options are available; this period will not exceed 4 months.

### Amendment 4, 06Jul-2017

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

As a result of the change in the duration of the optional extension period, the study objectives and associated statistical sections have been revised to include extension period time points.

Other protocol changes include:

- In view of the results of the thorough QT study CLCI699C2105, which showed that the increase in QTcF caused by LCI699 at therapeutic doses is below the threshold of regulatory concern, the QT-specific concomitant medication guidance for LCI699 was revised to limit the list of prohibited drugs to medications with a "Known risk to cause TdP" and "Possible risk to cause TdP", instead of all drugs known to prolong QT. This change is also in alignment with the terminology used in the QT Drug Lists (CredibleMeds®).The risks section was updated to include neutropenia, which is a known effect related to the decrease of cortisol in patients with Cushing's disease, in line with cases observed in clinical trials with LCI699.

### Amendment 5, 29-Jun-2018

The main purpose of this amendment is to increase the maximum duration of the optional extension period by one additional year in order to provide continued access to the study drug for those patients benefitting from the treatment until a separate long-term follow-up study is available at participating sites.

### Changes to the protocol

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

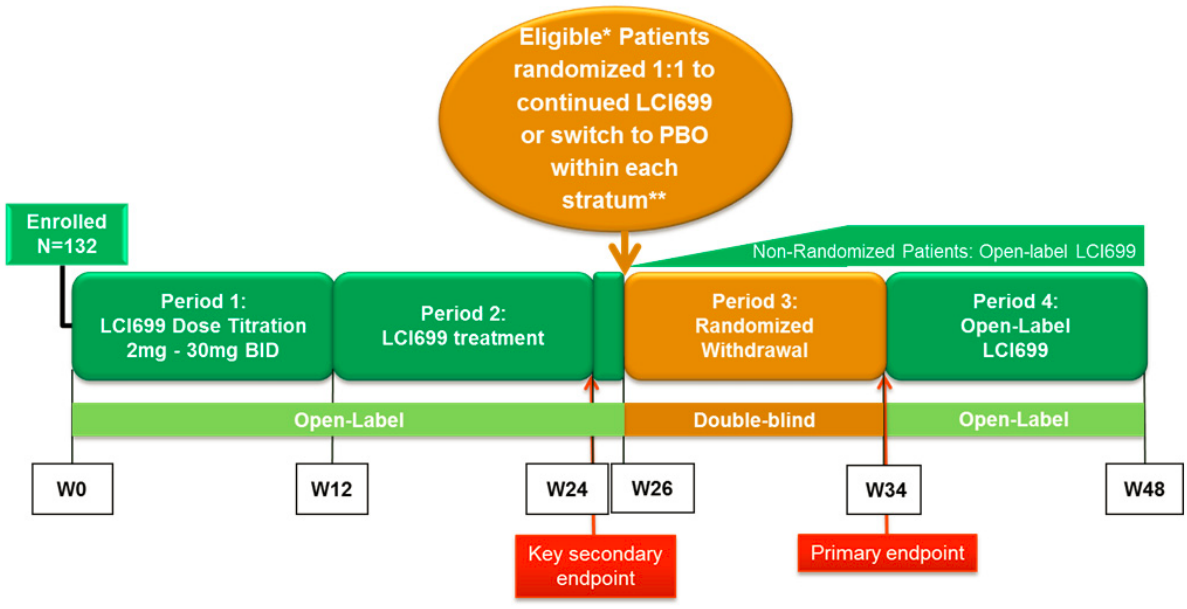
- Glossary of terms, Section 7.1.6: the definition of the Personal Data and Withdrawal of Consent has been updated in line with the latest Novartis protocol template updated following the release of the General Data Protection Requirements (GDPR) in the European Economic Area (EEA).
- List of abbreviations, Section 4.1.3.1, Section 6.5.2 and Section 6.5.3: Drug Supply Management replaced with Global Clinical Supply as per name change at Novartis.
- Protocol Summary, Section 6.1, Section 6.6.1, Table 6-3 and Table 6-4: clarified as 20 mg tablets supplied depending on availability.

- Section 4.1.5, Section 6.1.5: revised to extend the duration of the optional extension period and study and to include the transition timeframe to the long-term safety follow-up study or local alternative treatment option.
- Section 4.3: revised to extend the duration of the optional extension period and study.
- Section 6.5.3: corrected that the bioanalyst and the bioanalytical study monitor will also be unblinded in line with Novartis standards.
- Section 7.1.1 and Table 7-1: reference added to the Inclusion/Exclusion criteria for the eligibility assessment at screening.
- Section 7.2.1.3: revised as there was an incorrect reference to the BMI matching for the BMD T-score.
- Section 7.2.2.5, Section 10.5.3: added the central Pituitary MRI/CT assessment for tumor re-occurrence and tumor invasiveness.
- Section 7.2.3.2: corrected as placebo samples will be analyzed for this trial.
- Section 10: clarified that in this section SAS stands for Statistical Analysis System.

## 1.2 Study design

This is a Phase III, multi-center, double-blind, randomized withdrawal study following a 24 week, single-arm, open-label dose titration and treatment period to evaluate the safety and efficacy of LCI699 for the treatment of patients with Cushing's disease. The study has a core phase (consists of four study periods 1-4, see schematic diagram below) and an optional extension period, which are described below.

**Figure 1-1 Schematic of core study design**

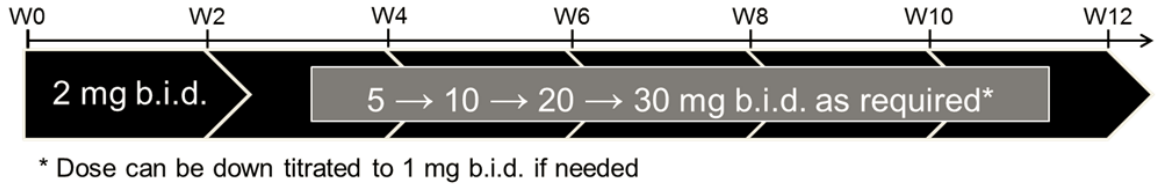



*To be eligible for randomization, the patient must have mUFC ≤ ULN at Week 24, and no further dose increase after Week 12.
**Strata are determined by the combination of two stratification factors at randomization: 1) LCI699 dose at Week 24 (≤ 5mg bid vs. > 5mg bid), and 2)history of pituitary irradiation (yes/no).

### 1.2.1 Study Period 1

This single-arm, open-label LCI699 period (Week 1 to Week 12) is the individual patient dose titration period.

**Figure 1-2 Schematic of study period 1**




Dose adjustments are based on the mean of three 24-hour UFC (mUFC) values as measured by the central lab. The triplicate urine samples are collected every two weeks during individual dose titration with the last urine sample preferably collected the day prior to the visit at site. The dose is increased if mUFC is above normal (> ULN). The dose is reduced if mUFC < LLN, or if the patient is symptomatic and mUFC is in the lower part of the normal range. The dose should be maintained if mUFC is within the normal range and the patient does not have signs or symptoms of adrenal insufficiency. At Week 0 and Week 2, dose increase is not permitted.

### 1.2.2 Study Period 2

This period (Week 13 to Week 26) aims to assess the efficacy and safety of LCI699 at the therapeutic dose determined during the dose titration period. Patients whose mUFC becomes elevated during this period can have their LCI699 dose increased further, if it is tolerated and the maximum dose of 30 mg b.i.d. has not been reached. Such patients will be followed for long-term safety but will not be considered complete responders, and cannot be randomized. Dose reductions and temporary dose interruptions for safety reasons are permitted during this period without affecting eligibility for randomization.

In order for a patient to be classified as a complete responder at Week 24, the following two conditions must be met: 1) mUFC ≤ ULN based on urine samples collected at Week 24; 2) LCI699 dose during Study Period 2 (Weeks 13-24) was not increased above the level established at the end of Study Period 1 (Week 12; end of individual dose titration period). Dose reductions and temporary dose interruptions for reasons of safety do not preclude the possibility of complete response assessment at Week 24.

The key secondary endpoint, the proportion of patients with a complete response (mUFC ≤ ULN), is assessed at Week 24.

Patients remain on open-label LCI699 during the period between week 24 and week 26, in order to ensure that sufficient time is allowed for central laboratory results (Week 24 mUFC) to become available for all patients at all sites, and to standardize the time of randomization across sites.

### 1.2.3 Study Period 3

Study Period 3 is a double-blind, placebo-controlled randomized withdrawal period (Week 26 to Week 34).

**Double blinding**

The Novartis study team, the patient, the investigator, and all other site staff remain blinded to treatment assignment from the time of randomization to the time of DBL for the core phase of the study.

The study was unblinded at the time of the core phase DBL, which occurred on 10-May-2018.

**Eligibility for randomization**

In order to be eligible for randomization, patients must have completed dose titration during the first 12 weeks, continued on LCI699 treatment with no further dose increase during Weeks 13-24, and have normal UFC (mUFC $\leq$ ULN) from urine samples collected at Week 24. Randomization is implemented at the Week 26 visit.

Patients that are not eligible for randomization are followed on open-label LCI699 until the end of the core treatment (Week 48), unless there is a reason to discontinue from the study prematurely.

**Randomization**

Eligible patients are randomized in a double-blinded fashion at Week 26 at a 1:1 ratio either to continue treatment with LCI699 at the same dose or to matching placebo. Patients are stratified at randomization according to: LCI699 dose at Week 24 ($\leq$ 5mg b.i.d. vs. $>$ 5 mg b.i.d.), and history of pituitary irradiation (yes/no).

**UFC monitoring during randomized withdrawal**

During the 8-week randomized withdrawal study period, mUFC is measured at scheduled visits every 2 weeks. However, patients are also allowed to have unscheduled visits at any time during the randomized withdrawal period if they report symptoms of hypercortisolism or hypocortisolism. The investigator decides the dose of study drug (LCI699 or placebo) during this period, although is blinded to treatment assignment. All laboratory tests during the randomized withdrawal period must be sent to the central laboratory for analysis, and all treatment decisions must be based on central laboratory results.

**Dose adjustments during randomized withdrawal**

The dose of study drug (LCI699 or placebo) should remain unchanged for patients that maintain a normal mUFC and do not develop AE's related to study drug during randomized withdrawal. The investigator may reduce or withhold a dose of study drug for safety reasons at any time during the study, including the randomized withdrawal period. Dose reductions or interruptions

for safety reasons during the randomized withdrawal period do not preclude the possibility of a complete response at Week 34. Dose increases are not permitted during the randomized withdrawal period.

**Discontinuation from randomized withdrawal**

During the randomized withdrawal study period, the patient must be discontinued from the randomized withdrawal period, declared a non-responder, if the mUFC increases to > 1.5 x ULN, and at least 2 individual urine samples show UFC > 1.5 x ULN at a single visit (scheduled or unscheduled).

After discontinuation from randomized withdrawal, or at the end of the randomized withdrawal period (Week 34), whichever comes first, the patient resumes open-label LCI699 at a dose selected by the investigator.

Patients who are discontinued from the study during the randomized withdrawal period are no longer in the study, and consequently they are not permitted to receive open-label LCI699 and cannot move forward to Study Period 4.

### 1.2.4 Study Period 4

Study Period 4 is a single-arm, open-label therapy (Week 35 to Week 48). After Week 34 visit, all patients receive open-label LCI699 treatment until Week 48. Dose changes are permitted. At Week 48, patients have the option to enter an extension period or discontinue LCI699 at week 48 to conclude with an end of core study visit 4 weeks off study drug (at Week 52).

### 1.2.5 Optional extension period

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 optional extension period will end after all patients have completed Week 72 or have discontinued early (prior to Week 72).

Study CLCI699C2301 ends when all ongoing patients have transitioned to the long-term safety follow-up study or have been offered local alternative treatment options; this period will not exceed 4 months after all ongoing patients have completed Week 72. Patients who continue to benefit from treatment and have completed Week 72 will be offered participation in a separate long-term safety follow-up study after the database lock of the core phase is completed.

If the long-term safety follow-up study is opened at site, patients should transition to the long-term safety follow-up study. If this option is not available, the patient can either be offered a local alternative treatment option or stay in the study until the study end (i.e. 4 months after the last patient completes Week 72) Patients entering the long-term safety follow-up study will complete an EOT visit. For these patients, the EOS visit is not applicable, as treatment on LCI699 will not be interrupted. Patients not entering the long-term safety follow-up study will complete an EOT visit, and an EOS visit 30 days after the last dose administration.

## 1.3 Study objectives and endpoints

The following table displays the study objectives/endpoints and the sections of this SAP document that describe the corresponding analyses.

For the Final CSR, not all study objectives will be reported. This is documented in the corresponding SAP section for each objective.

**Table 1-1 Study Objectives and endpoints**

| Objective | Endpoint | Analysis Section |
|---|---|---|
| **Primary** | | |
| To compare the complete response rate at the end of the 8-week period of randomized withdrawal (Week 34) between patients randomized to continued LCI699 therapy vs. placebo. | Proportion of randomized patients in each arm with: mUFC ≤ ULN at the end of 8 weeks of randomized withdrawal (Week 34), and were neither discontinued, nor had LCI699 dose increase above the level at week 26 during the randomized withdrawal period. | 2.5 |
| **Key secondary** | | |
| To assess the complete response rate at the end of individual dose-titration and treatment with LCI699 in the initial single-arm, open label period (Week 24). | Proportion of enrolled patients with mUFC ≤ ULN at Week 24 and had no dose increase above the level established at Week 12 between Week 13 and Week 24. | 2.6 |
| **Other secondary** | | |
| To compare the time-to-last control of mUFC during the randomized withdrawal period between patients randomized to continued LCI699 therapy and placebo. | Time-to-last control of mUFC, which is defined as the time (in days) from randomization to the last mUFC collection that was ≤ ULN before early discontinuation or completion of randomized withdrawal period, whichever is earlier. | 2.7.1 |
| To assess the complete, partial, and overall response rate at Week 12, Week 24, Week 48, and at scheduled time points during the extension period and the last available assessment. | Complete response rate: proportion of enrolled patients with mUFC ≤ ULN at Week 12, Week 24, Week 48, and at scheduled time points during the extension period (provided adequate follow-up), and the last available assessment<br><br>Partial response rate: proportion of enrolled patients with ≥ 50% reduction from baseline in mUFC, but mUFC > ULN) at Week 12, Week 24, and Week 48, and at scheduled time points during the extension period (provided adequate follow-up), and the last available assessment<br>Overall response rate: proportion of enrolled patients with mUFC ≤ ULN or at least 50% reduction from baseline at Week 12, Week 24, Week 48, and at scheduled time points during the extension period (provided adequate follow-up), and the last available assessment | 2.7.2 |
| To assess the change in mUFC during the core and extension periods of the study. | • Actual and percentage change in mUFC from baseline to each post-baseline visit during the core and extension (provided adequate follow-up) at which UFC is collected | 2.7.3 |

| Objective | Endpoint | Analysis Section |
|---|---|---|
| | • Actual and percentage change in mUFC from the time of randomization (Week 26) to the end of the randomized withdrawal period (Week 34), or the last mUFC measurement prior to early discontinuation, whichever occurs earlier. | |
| To assess the change in cardiovascular-related parameters associated with Cushing's disease during the core and extension periods of the study. | • Actual and percentage change from baseline during the core and extension periods (provided adequate follow-up) of the study in: fasting glucose, HbA1c, fasting lipid profile, blood pressure, body weight, BMI and waist circumference<br>• Actual and percentage change from the randomization (Week 26) to the end of randomized withdrawal period (Week 34), or the last measurement available prior to early discontinuation, whichever occurs earlier (see bullet above for individual parameters). | 2.7.4 |
| To assess the change from baseline in the physical features of Cushing's disease by photography at Week 12, 24, 34, 48, and during the extension period. | Categorical change from baseline to Week 12, 24, 34, 48, during the extension at week 72 and EOT extension in each of the following clinical signs of Cushing's disease by photography: facial rubor, hirsutism, striae, supraclavicular fat pad, dorsal fat pad, proximal muscle wasting (atrophy), central (abdominal) obesity, and ecchymoses (bruises). | 2.7.5 |
| To assess the change from baseline in bone mineral density by DXA scan at the lumbar spine and total hip at Week 48 and the last available assessment. | Actual and percent change from baseline to Week 48 and the last available assessment in bone mineral density as measured by DXA scan at the lumbar spine and total hip | 2.7.6 |
| To assess the time-to-escape. | Time-to-escape is defined as the time (in days) from the first mUFC ≤ ULN to the first mUFC results > 1.5 x ULN with at least 2 individual UFC results > 1.5 x ULN. | 2.7.7 |
| To assess general safety and AEs of special interest | Adverse events and laboratory abnormalities will be assessed using the National Cancer Institute-Common Toxicology Criteria (NCI-CTC) grading scale (version 4.03).<br>AEs of special interest, as reported by the investigator, or by laboratory evaluation, ECG, Holter recording, and pituitary MRI. | 2.8 |
| To evaluate exposures of LCI699 in patients with Cushing's disease | Plasma concentrations (predose, 0.5 h, 1.5 h, and 3.5 h post-dose) of LCI699 | 2.9 |
| To assess the change in Patient-Reported Outcomes (Health-Related Quality of Life) during the core and extension periods of the study. | • Change in standardized score of CushingQoL (to include 2 subscale and total scores), Beck Depression Inventory-II, and EQ-5D-5L (utility index and VAS), from baseline to Week 24 and Week 48. | 2.11 |

| Objective | Endpoint | Analysis Section |
|---|---|---|
| | • Change in standardized score of CushingQoL (to include 2 subscale and total scores), Beck Depression Inventory-II, and EQ-5D-5L (utility index and VAS), from the randomization (Week 26) to the end of randomized withdrawal period (Week 34), or the last measurement prior to early discontinuation, whichever occurs earlier.<br>• Change from baseline in standardized score of CushingQoL (to include 2 subscale and total scores), Beck Depression Inventory-II, and EQ-5D-5L (utility index and VAS), from baseline to Week 72, 96 and the EOT extension | |

# 2 Statistical methods

## 2.1 Data analysis general information

Patients who discontinue study drug will be considered withdrawn from the study after the final visit assessments and the final safety follow-up visit are performed or when it is clear that the patient will not return for final visit assessments and/or final safety follow-up visit.

The analysis of the core phase, including the primary and key secondary analyses was performed based on cumulative data collected up to the date when all enrolled patients had either completed or prematurely withdrawn from the core phase of study. The results and outcomes of this analysis were presented in an interim CSR.

The study was powered based on the primary and key secondary analyses. All effiacy analyses presented in the Final CSR are considered as supportive, and no formal statistical testing will be performed.

Analysis for the Final CSR will be performed once all patients have either completed the extension period or discontinued earlier.

Data will be analyzed using the SAS System for data analysis V9.4 or higher.

### 2.1.1 General definitions

#### 2.1.1.1 Study day

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

The study day for an event that occurred 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 occurred after study day 1 will be calculated as (date of event – date of first administration of study drug) +1.

Study day will be displayed in the data listings.

#### 2.1.1.2 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 LCI699) is taken as the "baseline" assessment; the last available assessment within 21 days prior to the first dose of randomized treatment (LCI699 or Placebo) is taken as the "randomization" assessment; If patients have no value as defined above, the baseline/randomization result will be considered missing.

#### 2.1.1.3 Visit number

The time point (Day/Month) associated with an assessment will be determined by the visit number assigned to the assessment in the database. The mapping of visit numbers to time points in the core study and the extension study are provided in the table below.

**Table 2-1 Scheduled visits in core phase**

| Core study Visit | Day/Week | Clarifying Notes |
|---|---|---|
| Visit 1 | Day -35 to Day -8 | Screening |
| Visit 2 | Day -7 to Day -1 | Baseline |
| Visit 3 | Day 1/Week 0 | Dose escalation period |
| Visit 4 | Day 15/Week 2 | Dose escalation period |
| Visit 5 | Day 29/Week 4 | Dose escalation period |
| Visit 6 | Day 43/Week 6 | Dose escalation period |
| Visit 7 | Day 57/Week 8 | Dose escalation period |
| Visit 8 | Day 71/Week 10 | Dose escalation period |
| Visit 9 | Day 85/Week 12 | Dose escalation period |
| Visit 10 | Day 113/Week 16 | Treatment period |
| Visit 11 | Day 141/Week 20 | Treatment period |
| Visit 12 | Day 169/Week 24 | Treatment period |
| Visit 13 | Day 183/Week 26 | Randomized Withdrawal period |
| Visit 14 | Day 197/Week 28 | Randomized withdrawal period |
| Visit 15 | Day 211/Week 30 | Randomized withdrawal period |
| Visit 16 | Day 225/Week 32 | Randomized withdrawal period |
| Visit 17 | Day 239/Week 34 | Randomized withdrawal period |

| Core study Visit | Day/Week | Clarifying Notes |
|---|---|---|
| Visit 1 | Day -35 to Day -8 | Screening |
| Visit 18 | Day 253/Week 36 | Open Label period |
| Visit 19 | Day 281/Week 40 | Open Label period |
| Visit 20 | Day 309/Week 44 | Open Label period |

**Table 2-2 Scheduled visits in extension period**

| Extension study Visit | Day/Week | Clarifying Notes |
|---|---|---|
| Visit 21 | Day 337/Week 48 | Extension |
| Visit 22 | Day 365/Week 52 | Extension |
| Visit 23 | Day 393/Week 56 | Extension |
| Visit 24 | Day 421/Week 60 | Extension |
| Visit 25 | Day 449/Week 64 | Extension |
| Visit 26 | Day 477/Week 68 | Extension |
| Visit 27 | Day 505/Week 72 | Extension |
| Visit 28 | Day 589/Week 84 | Extension |
| Visit 29 | Day 673/Week 96 | Extension |
| Visit 30 | Day 757/Week 108 | Extension |
| Visit 31 | Day 841/Week 120 | Extension |
| ……. | Every 84 days/12 weeks | Extension |

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 778 (End-of-Treatment in extension period) are scheduled when the patient either completes the respective study period 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 (LASTVIS) prior to the 777/778 visit, then it will be mapped to the next scheduled visit (LASTVIS+1) in the visit schedule (from the tables above).

The 777/778 visit will be considered to have occurred neither too soon nor too late after the actual last scheduled visit if the number of days between the two visits is

(i) at least half of the planned gap between the patient's actual last scheduled visit (LASTVIS) and the next scheduled visit and

(ii) at most the total of (a) the planned gap between the patient's actual last scheduled visit (LASTVIS) and the next scheduled visit and (b) half of the planned gap between the patient's next two scheduled visits.

If the number of days between the 777/778 visit and LASTVIS is less than the range specified above then the 777/778 visit will be mapped to an unscheduled visit of LASTVIS; if it is more then it will be mapped to an unscheduled visit of LASTVIS + 1.

#### 2.1.1.4 Calculating mean UFC

To compute the mean UFC for a patient at any particular visit, at least two individual 24hr 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. The derived mUFC value, calculated by Novartis, will be used for all analyses.

#### 2.1.1.5 Study day associated with a mUFC assessment

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

#### 2.1.1.6 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

#### 2.1.1.7 Calculation of proportions of responders

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

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

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

2) patients who discontinued prior to the data cutoff date for the Final DBL will be included up to the furthest scheduled visit they could have completed if they had not discontinued early based on data cut off and last completed based on the date of last completed schedule visit and analyses cut-off date. For example, if the last completed scheduled visit for an early discontinued patient is Week 52, and the time between data cutoff and last completed scheduled visit is 8 weeks, he/she will be included in the analyses up to Week 60.

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

Patients randomized to placebo during the RW period, will not be included in the denominator for visits at which they received placebo.

#### 2.1.1.8 Method for calculating Confidence Intervals

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

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

#### 2.1.1.9 AE summary cutoff

All data up to data cut-off date will be at least listed. All safety data prior to the data cut-off will be summarized with the exception of AEs and deaths, which will follow the cut-off rule specified below.

AE/death summary cut-off date = min { data cut-off date, max(last dosing date + 30 , safety follow-up visit date) }

AEs/deaths that occur after the AE/death summary cut-off date but prior to the data cut-off date will be listed and flagged.

#### 2.1.1.10 Criteria of adequate follow-up for time points in the extension period

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

## 2.2 Analysis sets

**Full analysis set (FAS)**: comprises all enrolled patients who receive at least one dose of LCI699. FAS is used in efficacy analysis for study period other than RW period including key secondary endpoint.

**Safety set (SAS):** comprises all enrolled patients who received at least one dose of LCI699 and had at least one valid post-baseline safety assessment. Please note: the statement that a patient had no adverse events (on the Adverse Event CRF) constitutes a safety assessment.

**Per-Protocol set:** There are two per-protocol sets defined in this study.

- The Per-Protocol Set for Randomized Analysis Set (PPRAS) consists of a subset of the patients in the RAS who had no selected protocol deviations.
- The Per-Protocol Set for Full Analysis Set (PPFAS) consists of a subset of the patients in the FAS who had no selected protocol deviations.

PPFAS will only be used in supportive analyses for key secondary efficacy endpoint, while PPRAS will only be used in supportive analyses for primary efficacy endpoint. Details of protocol deviations that lead to exclusion from PPS and/or PPRAS can be found in table below.

**Table 2-3 Protocol deviations leading to exclusion from PPFAS and/or PPRAS**

| Protocol Deviation description | Protocol deviation Code(s) in VAP3 (Amendment 4, July2017) | Excluded from PPFAS? | Excluded from PPRAS? |
|---|---|---|---|
| Informed consent for core phase not documented | I01 | Yes | Yes |
| mUFC related inclusion criteria not met | I06/I07 | Yes | Yes |
| ACTH related inclusion criteria not met | I09 | Yes | Yes |
| Cushing's disease confirmation is missing | I10 | Yes | Yes |
| Pituitary surgery related inclusion criteria not met | I11/I12 | Yes | Yes |
| Pituitary irradiation related inclusion criteria not met | I14 | Yes | Yes |
| Washout period related inclusion criteria not met | I13/I15/I16/I17/I18/I19/I20 | Yes | Yes |

| | | | |
|---|---|---|---|
| Subject did not meet the eligibility criteria for randomization but was randomized at Week 26. | I21 | No | Yes |
| Participation in another trial with an investigational drug does meet the exclusion criteria | E01 | Yes | Yes |
| Subject pregnant or lactating at study entry | E04/E05 | Yes | Yes |
| Subject's history of hormone over secretion does meet the exclusion criteria | E10 | Yes | Yes |
| Subject's medical history of Cushing's syndrome does meet the exclusion criteria | E11 | Yes | Yes |
| Subject compliance history does meet the exclusion criteria | E23 | Yes | Yes |
| Subject met the discontinuation criteria, but was not discontinued from study treatment | D01/D02 | Yes* | Yes** |
| Subject took a prohibited concomitant medication | M01 | Yes* | Yes** |

*If protocol deviation happens before Week 24, when the key secondary endpoint is assessed

**If protocol deviation happens before end of randomized withdrawal period, when the primary endpoint is assessed

The analysis sets used for various analyses in the Final CSR are summarized below

**Table 2-4 Analysis sets used for specific analyses**

| | FAS | SAS | PPFAS/ PPRAS |
|---|---|---|---|
| Patient Disposition | X | | |
| Demography and baseline disease characteristics | X | | |
| Medical History | X | | |
| Prior Medication | X | | |
| Protocol Deviation | X | | |
| Concomitant Medications | | X | |
| Exposure to study medication | | X | |
| Efficacy analyses | X | | X* |
| Safety analyses | | X | |
| Patient-reported outcomes | X | | |

* PPFAS will only be used in supportive analyses for key secondary efficacy endpoint.
* PPRAS will only be used in supportive analyses for primary efficacy endpoint.

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

For patients in PPRAS

- LCI699 group: patients randomized to continued treatment of LCI699 for the randomized withdrawal period of the study
- Placebo group: patients randomized to placebo for the randomized withdrawal period of the study

For patients in FAS/PPFAS

- LCI699 group: patients randomized to continued treatment of LCI699 for the randomized withdrawal period of the study
- Placebo group: patients randomized to placebo for the randomized withdrawal period of the study
- Non-randomized patients: patients who do not enter randomized withdrawal period of the study (either discontinued study before the randomization or not eligible to be randomized)

For patients in SAS

- LCI699 group: patients receiving study treatment of LCI699 for the randomized withdrawal period of the study
- Placebo group: patients receiving study treatment of placebo for the randomized withdrawal period of the study
- Non-randomized patients: patients who do not enter randomized withdrawal period of the study (either discontinued study before the randomization or not eligible to be randomized)

### 2.2.1 Subgroup of interest

Subgroups of interest for this study include the two stratification factors for randomization

History of pituitary irradiation: Yes and No

LCI699 dose at Week24: ≤ 5mg b.i.d. and > 5mg b.i.d.

For the Final CSR, the per-protocol analysis of the primary effiacy endpoint will be performed including adjustment for the two stratification factors.

## 2.3 Patient disposition, demographics and other baseline characteristics

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 in Section 2.2.

### 2.3.1 Patient disposition

For overall study period, counts of patients for the following items will be summarized by treatment group using FAS:

- discontinued at any time*
- Primary reason for discontinuation at any time

- discontinued at or prior to Week 12
- Primary reason for discontinuation at or prior to Week 12
- discontinued at or prior to Week 24 but after Week 12
- Primary reason for discontinuation at or prior to Week 24 but after Week 12
- discontinued prior to Week 48 but after Week 24
- Primary reason for discontinuation prior to Week 48 but after Week 24
- Completed Week 48
  - Completed Week 48 and did not enter Extension period
  - Completed Week 48 and enter Extension period
- Ongoing in Extension
- Discontinuation in the Extension
- Primary reason for discontinuation in the Extension
- Discontinued at or prior to Week 72 but after Week 48
- Discontinued prior to Week 96 but after Week 72
- Discontinued after Week 96
- Completed extension

* Patients who completed Week 48 and declined to enter optional extension period are not counted as discontinuations.

For randomized withdrawal period, counts of patients for the following items will be provided in a separate disposition summaries presented by treatment group using RAS:

- discontinued from randomized treatment before completing RW period
- primary reason for discontinuation before completing RW period
- discontinued from randomized treatment at or prior to Week 28
- primary reason for discontinuation at or prior to Week 28
- discontinued from randomized treatment at or prior to Week 30 but after Week 28
- primary reason for discontinuation at or prior to Week 30 but after Week 28
- discontinued from randomized treatment at or prior to Week 32 but after Week 30
- primary reason for discontinuation at or prior to Week 32 but after Week 30
- discontinued from randomized treatment at or prior to Week 34 but after Week 32
- primary reason for discontinuation at or prior to Week 34 but after Week 32
- Completed the RW period (Week 34)

### 2.3.2 Demographic and baseline disease characteristics

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

### 2.3.3 Medical history

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

### 2.3.4 Protocol deviations

The number and percentage of patients with any PDs up to data cutoff will be tabulated by treatment group using FAS.

PDs leading to exclusion from the PPFAS and PPRAS will be tabulated by treatment group using FAS and RAS respectively.

All PDs up to data cutoff will be listed.

The criteria for protocol deviation are specified in Validation and Planning (VAP) Module 3 and will be finalized prior to database lock.

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

### 2.4.1 Study treatment / compliance

In the Final CSR the exposure to the study drug will be summarized for the overall study period only, using the SAS.

**Duration of exposure**

• For overall study period, duration of exposure to LCI699 for patients in the SAS is calculated as below:

- •for Placebo group:

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

- •for LCI group and non-randomized patients

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

The above duration calculation includes the periods of temporary interruption.

**Dose reduction/interruption**

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

The actual and planned doses administered and reason for dose change will be listed with UFC information.

**Dose of LCI699**

The LCI699 average total daily dose by visit during the overall study period will be summarized using descriptive statistics and displayed graphically. Dose levels whilst on placebo, for patients randomized to placebo during the RW period, will not be included in the calculations.

### 2.4.2 Prior, concomitant and post therapies

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

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

Concomitant medications and significant non-drug therapies will be listed and summarized using frequency counts and percentages by ATC class, preferred term and treatment group within each of three study periods: first 26 weeks (FAS), randomized withdrawal period (RAS), and overall study period (FAS).

Therapies for Cushing's Disease taken prior to first dose of LCI699 will be summarized using frequency counts and percentages by ATC class, preferred term and treatment group.

If the start date of a concomitant medication is missing or partially missing, then it will be imputed following Novartis standard rule for table and listing.

## 2.5 Analysis of the primary objective

The primary objective was to compare the complete response rates at the end of the 8 weeks period of randomized withdrawal (Week 34) between patients randomized to continued LCI699 therapy vs. placebo.

The primary efficacy variable is the proportion of randomized patients in each treatment arm that are complete responders at the end of the 8 weeks of the randomized withdrawal period (Week 34). A complete responder is defined as a patient who has mUFC $\leq$ ULN (based on central laboratory result) at Week 34 and who was neither discontinued nor had LCI699 dose increase above the level at week 26 during the randomized withdrawal period of the study. Patients who discontinued during the randomized withdrawal period will be counted as non-responders for the primary endpoint. Dose reductions and temporary dose interruptions for safety reason during randomized withdrawal period do not preclude patients from being complete responder for primary endpoint.

For the primary objective, the statistical null hypothesis states that the complete response rates at the end of 8-week randomized withdrawal period (i.e., at Week 34) are the same between the two randomized arms. To test this hypothesis, a Cochran–Mantel–Haenszel exact test stratified by the two stratification factors considered for randomization will be performed using the RAS following the intent-to-treat principle.

If the 2-sided p-value is $\leq 0.05$ and the odds ratio (LCI699 vs. Placebo) is $> 1$, the null hypothesis will be rejected and the complete response rate in the LCI699 arm will be considered higher than that in the placebo arm.

As a supportive analysis to this analysis, 1) an un-stratified Fisher's exact test of the primary endpoint will also be performed using RAS; 2) both stratified CMH exact test and un-stratified Fisher's exact test of the primary endpoint will be performed using PPRAS.

After the interim CSR was published, additional protocol deviations were reported which affect the per-protocol population used to perform the per-protocol analyses of the primary endpoint, therefore the Final CSR will report the updated result of the supportive analyses using the PPRAS.

The analyses of the primary endpoint using the RAS are not impacted by these additional protocol deviations, and therefore will not be reported in the Final CSR.

## 2.6 Analysis of the key secondary objective

The key secondary objective was to assess the complete response rate at the end of 24 weeks of dose-titration and treatment with LCI699 in the initial single-arm, open label part of this trial.

The key secondary efficacy variable is the proportion of complete responders at Week 24. A complete responder is defined as an enrolled patient who has mUFC $\leq$ ULN at Week 24 and the dose of LCI699 during Study Period 2 (Weeks 13-24) was not increased above the level established at the end of Study Period 1 (Week 12). Dose reductions and temporary dose interruptions for safety reasons do not preclude patients from being complete responder for the key secondary endpoint. Enrolled patients who had missing mUFC assessment at Week 24 will be counted as non-responders for the key secondary endpoint.

For the key secondary objective, the statistical null hypothesis states that the complete response rate at week 24 LCI699 is $\leq 30\%$. The analysis of the key secondary objective will be based on the 2-sided 95% exact confidence interval (Clopper-Pearson method). If the lower bound of this 95% confidence interval is $\geq 30\%$, the null hypothesis will be rejected and the complete response rate will be considered at least 30% after 24 weeks of treatment with LCI699.

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

The above analysis of the key secondary endpoint will be performed using FAS. As supportive analysis, same analysis will be performed using PPFAS.

After the interim CSR was published, additional protocol deviations were reported which affect the per-protocol population used to perform the per-protocol analyses of the key secondary

endpoint, therefore the Final CSR will report the updated result of the supportive analyses using the PPFAS.

The analyses of the key secondary endpoint using the FAS are not impacted by these additional protocol deviations, and therefore will not be reported in the Final CSR.

## 2.7 Analysis of secondary efficacy objectives

For the objectives identified below, the definition of Baseline/Randomization assessment and the method of computing confidence intervals are specified in Section 2.1.1.2 and Section 2.1.1.8 respectively. Last observation carried forward (LOCF) method will not be used in any of these analyses. For analysis using FAS, results will be presented by LCI699 group, Placebo group, Non-randomized patients, and All patients.

### 2.7.1 Compare the time-to-last control of mUFC during the randomized withdrawal period between patients randomized to continued LCI699 and placebo

The results of this objective were reported in the interim CSR, and will not be repeated for the Final CSR.

### 2.7.2 Assess the complete, partial, and overall response rate at Week 12, Week 24, Week 48, and during the extension period

The proportion of complete responders (enrolled patients with mUFC ≤ ULN), partial responders (enrolled patients with mUFC > ULN and at least 50% reduction from baseline), and overall responders (enrolled patients with mUFC ≤ ULN or have at least 50% reduction from baseline) will be summarized using point estimates for every scheduled visit in the core and extension (provided adequate follow-up) at which UFC is collected. 95% 2-sided CIs for response rates will be provided for Week 48, Week 60, Week 72 and the last available assessment of the study. The FAS will be used for the analyses.

### 2.7.3 Assess the change in mUFC during the core and extension period of study

For the actual value and change in mUFC from baseline during the overall study period, descriptive summaries will be provided for every scheduled visit in the core and extension (provided adequate follow-up) at which UFC is collected. The FAS will be used for the analysis.

Patients randomized to placebo during the RW period, will not have their mUFC values included in the analysis for visits at which they received placebo.

### 2.7.4 Assess the change in cardiovascular-related metabolic parameters associated with Cushing's disease during the core and extension period of the study

The following parameters will be analyzed: glucose, HbA1c, fasting lipid profile, SBP, DBP, weight, waist circumference and BMI).

For the actual value and change from baseline during the overall study period, descriptive summaries will be provided for every scheduled visit in the core and extension (provided adequate follow-up). The FAS will be used for the analysis.
Patients randomized to placebo during the RW period, will not have their values included in the analysis for visits at which they received placebo.

### 2.7.5 Assess the change from baseline in physical features of Cushing's disease by photography

For physical features of Cushing's disease, such as facial rubor, hirsutism, striae, supraclavicular fat pad, dorsal fat pad, proximal muscle wasting (atrophy), central (abdominal) obesity, and ecchymoses (bruises), the change from baseline (captured by a semi-quantitative Likert scale) at visits where photography is scheduled (Week 12, 24, 34 and 48 as well as Week 72 and EOT extension) will be assessed by shift tables. In addition, the proportion of patients having a favorable shift from baseline at post-baseline time points will also be tabulated. The FAS will be used for the analyses.

### 2.7.6 Assess the change from baseline in bone mineral density by DXA scan at Week 48 and the last available assessment

For bone mineral density measured by DXA scan at the lumbar spine and total hip, descriptive summaries of actual and percentage change from baseline at Week 48 and the last available assessment will be provided. The FAS will be used for the analysis.

### 2.7.7 Assess the time-to-escape under treatment of LCI699

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

- prior normalization of UFC has occurred (mUFC≤ ULN)
- both the mUFC and at least 2 individual values contributing to that mUFC have to be >1.5 x ULN
- the loss of control of UFC is not related to a dose interruption or dose reduction due to safety reasons
- happens beyond 12-week dose titration period (Study Period 1).

Time-to-escape is defined as the time (in days) between the first UFC assessment with mUFC ≤ ULN and either the UFC assessment of escape (event) or last UFC assessment before permanent discontinuation of LCI699 treatment (censored), whichever occurs earlier.

For patients who attained normalization of UFC (mUFC ≤ ULN), time-to-escape will be analyzed using K-M plot. The quartiles of time to escape and corresponding two-sided 95% confidence interval will be calculated using Kaplan-Meier methodology. In addition, time-to-escape will be summarized using descriptive statistics for patients who escape. FAS will be used for the analysis.

Patients randomized to placebo are not included in this analysis.

## 2.8 Safety analyses

The assessment of safety will be based mainly on the frequency of adverse events and on the number of laboratory values that fall outside the pre-determined ranges. Other safety data (e.g. electrocardiogram, vital signs, and special tests) will also be presented.

In the Final CSR results for the overall study period will be analyzed, using the SAS. Results will be presented by Randomized patients, Non-randomized patients and All patients.

The safety results for the Final CSR will focus solely on the safety of LCI699. Therefore scheduled safety assessments performed whilst on placebo, for patients randomized to placebo during the RW period, will not be included. Similarly, adverse events with a start date which corresponds to when a patient was receiving placebo will not be included in adverse event summaries.

### 2.8.1 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.

#### 2.8.1.1 Coding of AEs

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.

#### 2.8.1.2 Grading of AEs

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 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

#### 2.8.1.3 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) but no later than AE summary cutoff defined in Section 2.1.1.9. 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".

The frequency of CTC grades 3 and 4 AEs will be summarized separately.

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

Adverse events with a start date which corresponds to when a patient was receiving placebo will not be included in adverse event summaries.

#### 2.8.1.4 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
- Adverse events, suspected to be study drug related, by primary system organ class, preferred term and maximum CTC grade
- Adverse events, regardless of study drug relationship, by preferred term
- Adverse events, suspected to be study drug related, by preferred term
- All 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
- Serious adverse events,suspected to be study drug related, by primary system organ class, preferred term and maximum CTC grade
- Serious adverse events, regardless of study drug relationship, by preferred term and treatment
- 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
- Serious adverse events leading to study drug discontinuation, regardless of study drug relationship, by primary system organ class and preferred term

- Adverse events of Special Interest, regardless of study drug relationship, by category and preferred term
- Adverse events of Special Interest with suspected study drug relationship, by category and preferred term
- Adverse events of special interest leading to study drug discontinuation, regardless of study drug relationship, by category, and preferred term
- Adverse events of special interest requiring dose adjustment or interruption, regardless of study drug relationship, by category, and preferred term
- On-treatment deaths and serious adverse events by system organ class and preferred term
- Non-serious adverse events (threshold = 5%) by system organ class and preferred term

#### 2.8.1.5 Adverse events of special interest / grouping of AEs

Groupings of AEs of special interest consist of adverse events for which there is a specific clinical interest in connection with LCI699 treatment (i.e. where LCI699 may influence a common mechanism of action responsible for triggering them) or adverse events which are similar in nature (although not identical). The list of AESIs is updated periodically after MedDRA update and/or review of accumulating trial data, and stored on the eCRS platform. The results for the Final CSR will use the list in place at the time of DBL.

#### 2.8.1.6 Adverse events by time of onset

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

The time periods used will be

- Baseline to Week 26
- Week 26 to Week 48
- Week 48 to Week 72
- Week 72 onwards

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

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

### 2.8.2 Deaths

Deaths will be reported, by primary system organ class and preferred term. Patients will not be followed-up for survival in this study, with patients considered to be off-treatment 30 days after treatment discontinuation.

### 2.8.3 Laboratory data

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 Periods through the last study visit.

Eligible laboratory data will be classified into CTC grades according to NCI 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.

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

- 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 from baseline to the worst post-baseline value and from baseline to the last post-baseline values using CTC grades will be produced for hematology, biochemistry, and urine laboratory parameters with CTC grades
- For laboratory parameters in which CTC grades are not defined, shift tables from baseline to the worst post-baseline value and from baseline to the last post-baseline values will be produced using the low/normal/high classifications based on laboratory reference ranges
- Shift tables of fasting blood glucose and HbA1c from baseline to the highest post-baseline value and from baseline to the last post-baseline values using the ADA (2010) classification.
- Selected laboratory data will be also be displayed by presenting summary statistics of change from baseline value.

### 2.8.4 Other safety data

#### 2.8.4.1 ECG and cardiac imaging data

Fridericia's formula (QTcF) will be used to calculate the heart rate-corrected QT interval (ms) based on the heart rate (HR bpm) and QT (ms) for centrally-read data. These calculated QTc values will be used in ECG summary tables and listings. The formula is as follows:

$QTcF\ (\text{in ms}) = QT/(RR)^{1/3}$

The following analyses will be performed for variables PR, QRS, QT interval, heart rate, and QTcF (Fridericia's) for the overall study period:

- summary statistics at baseline, all post-baseline time points as well as corresponding change from baseline.

- For randomized withdrawal period: summary statistics at randomization, all time points within randomized withdrawal period as well as corresponding changes from randomization
- Listing of ECG data including all scheduled and unscheduled time points

No imputation of missing data will be performed.

The number and percentage of patients with notable ECG interval values will be summarized.

A newly occurring ECG finding is defined as an notable finding at post-baseline that is not present at baseline.

The notable criteria for PR are

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

The notable criteria for QRS are

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

The notable criteria for QT and QTcF are

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

The percentage of patients having notable ECG interval values is based on the total number of patients who are at risk for a specific category. For new abnormality post-baseline values, this is the number of patients with both baseline and post-baseline evaluations who are normal at baseline. For abnormal change from baseline, this is the number of patients with both baseline and post baseline evaluations. A subject with multiple occurrences of a newly occurring abnormality is counted only once per abnormality.

All ECG data will be listed. If corrected QTcF are provided (providing them is optional), they will be listed in addition to the values derived using the formulae above. (In the summaries only the derived values will be used.) The patients with notable ECG interval values will be listed and the corresponding notable values will be flagged in the listings.

For 24hr Holter assessment, summaries of the key parameters will be provided. The worst observed post-baseline value for each patient, for each parameter will be presented.

The following parameters will be presented using shift tables

- % of patients with maximum HR >100 bpm
- % of patients with minimum HR <40 bpm
- % of patients with average HR >90 bpm

- % of patients with total SVEs >200
- % of patients with total VEs >200

The following parameters will be presented as change from baseline

- Total number of pauses >2 seconds
- Total SVE run events
- Total VE run events

To ensure accurate reporting of results, only Holter assessments which were performed for at least 20 hours will be used in any analysis.

All 24hr summary results will also be listed for the reported assessments.

#### 2.8.4.2 Vital signs

All vital signs data (weight (kg), body temperature ($^0$C), pulse rate (beats per minute), and 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, triplicate measurements are planned when assessed, and the mean of available values will be taken for analysis purposes. Change over time from baseline will be summarized.

The criteria for clinically notable abnormalities are defined as follows:

**Clinically notable elevated values**

- Systolic BP: ≥ 180 mmHg and an increase ≥ 20 mmHg from baseline
- Diastolic BP: ≥ 105 mmHg and an increase ≥ 15 mmHg from baseline.
- Pulse: ≥ 120 bpm with increase from baseline ≥15 bpm
- Weight: Increase from baseline of ≥ 10%
- Temperature: Increase from baseline of ≥ 39.1$^0$C

**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
- Pulse: ≤ 50 bpm with decrease from baseline ≥ 15 bpm
- Weight: Decrease from baseline of ≥ 5%

#### 2.8.4.3 Tumor volume

For tumor volume evaluated by MRI (or CT) scanning in patients with detectable tumor volume at baseline, descriptive summary of actual tumor volumes as well as its change from baseline will be provided at visits where evaluation is scheduled (Week 24, 48, 72 and any further visits

occurring every 24 weeks). For MRI (or CT) images that are not interpretable for tumor volume, the longest dimension (in mm) will be listed instead.

Tumor invasiveness at each scheduled visit, and the change in status from baseline will be reported.

The proportion of patients with measurable tumors at each visit, and the change in status from baseline will be reported.

## 2.9 Pharmacokinetic endpoints

No PK analysis will be performed for the Final CSR.

## 2.10 PD and PK/PD analyses

No PK/PD analysis will be performed for the Final CSR.

## 2.11 Patient-reported outcomes

The Cushing's QoL score (both the total score and two subscale scores) is identified as the primary PRO variable of interest. EQ-5D-5L utility index and visual analogue scale (VAS) scores, and Beck Depression Inventory-II (BDI-II) total score, are identified as secondary PRO variables of interest.

### 2.11.1 CushingQoL

The CushingQoL is a valid and reliable disease-specific QoL questionnaire which assesses health-related quality of life (HRQoL) in patients with Cushing's syndrome and has been validated in patients with Cushing's disease (Webb SM, 2008; Nelson L., 2013). The CushingQoL consists of questions reflecting dimensions of HRQoL related to physical aspects (e.g. 'I bruise easily'), psychological aspects (e.g. 'I am more irritable, I have sudden mood swings and angry outbursts'), and social aspects (e.g. 'I have had to give up my social or leisure activities due to my illness').

The questionnaire consists of 12 items measured on a five point Likert-type scale assessing how often ('always' to 'never') or how much ('very much' to 'not at all') each item has been related to the patient's Cushing's disease in the previous 4 weeks. Scoring of each item ranges from 1 ('Always' or 'Very much') to 5 ('Never' or 'not at all'). For the purpose of the clinical trial, the recall period has been modified to 'within the past week' in order to be more sensitive to the changes in patient HRQoL, specifically during the randomized withdrawal period, where it is believed that changes in Cushing's disease symptoms will occur rapidly once patients withdrawal from LCI699 treatment

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

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

$[(X – L) / (H – L)] * 100$

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

Recent research recommends that a 2 sub-scale scoring (namely, a *psychosocial issues scale* and a *physical problems scale*) provides the optimal interpretation, rather than the total score. (Tiemensma J. 2016). The CushingQoL 2 sub-scale scoring of each subscale is exactly the same as the total score. The items which comprise each subscale are shown in the table below:

Table 2-4 Items for the two subscales of CushingQoL

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

Currently a minimal important difference (MID) of 10.1 is defined in the literature based on the distribution method of a 0.5 SD unit change using baseline data, with the original 4 week recall period (Nelson, 2013, Norman, 2003). However, anchor-based methods for calculating MIDs have been referenced as more reliable estimates for interpreting change in PRO scores over time (based on an individual's level of change rather than a group level of change) in PRO guidelines (FDA, 2009). Given the importance of anchor-based MIDs and that the recall period has been modified to 1 week, the MID will be derived by Novartis from data collected in previous clinical trial(s) using the CushingQoL, as possible, and analyses of the present clinical trial data will then be performed for confirmatory purposes for this anchor-based MID (as possible). The proportion of patients whose CushingQoL standardized score change from baseline by at least the newly derived MID and the associated 95% CI will be summarized by study period and group (specifically for study period 3 analyses).

### 2.11.2 BDI-II

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

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

Minimal range = 0-13
Mild depression = 14-19
Moderate depression = 20-28
Severe depression = 29-63

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

### 2.11.3 EQ-5D-5L

Health status will be assessed using the EQ-5D-5L. The EQ-5D-5L has two components, the EQ-5D-5L descriptive system and the EQ-5D-5L visual analog scale (VAS) (Herdman, M., 2011, The EuroQoL Group, 2013). The EQ-5D-5L descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five levels: 'no problems', 'slight problems', 'moderate problems', 'severe problems' and 'unable to do activity or extreme problems'. A utility index can be computed from the EQ-5D-5L descriptive system with utility scores ranging from -0.281 (worst imaginable health state) to 1 (best imaginable health state), with -0.281 representing an "unconscious" health state. The EQ-5D-5L VAS records the subject's self-rated health state on a 100-point vertical VAS (0=worst imaginable health state; 100=best imaginable health state) (The EuroQoL Group, 1990) A score difference of 0.037-0.069 for the EQ-5D-5L utility score will be used as MID (McClure, 2017). A score difference of 7 for the EQ-5D-5L VAS will be used as MID estimates for the EQ-5D-5L (Pickard, 2007).

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

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

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

### 2.11.4 Secondary objective - Assess the change in Patient-Reported Outcomes (Health-Related Quality of Life) during the core and extension period of the study

Changes in PRO that are either statistically significant (based on two-sided 95% confidence interval with no adjustment for multiplicity) or exceeding the MID will be flagged.

For each of four PRO variables (CushingQoL score (2 subscale and total score), BDI total score, EQ-5D-5L utility index, and EQ-5D-5L VAS score), descriptive summaries of the actual value and change from baseline during the overall study period will be provided. The FAS will be used for this analysis.

## 2.12 Biomarkers

No biomarker analyses will be performed for the Final CSR.

## 2.13 Other Exploratory analyses

No exploratory analyses will be performed for the Final CSR.

## 2.14 Interim analysis

The study has no planned interim analysis for efficacy.

# 3 Sample size calculation

The sample size calculation relates to the primary and key secondary efficacy analyses, which will not be reported in the Final CSR.

## 3.1 Sample size justification

Eligible patients will be stratified at randomization according to: LCI699 dose at Week 24 (≤ 5mg bid vs. > 5mg bid); and history of pituitary irradiation (yes/no). It is estimated that 10 %, 40%, 10% and 40 % of randomized patients respectively will be in the 4 strata defined by two randomization stratification factors (≤ 5mg b.i.d and Yes; ≤ 5mg b.i.d and No; > 5mg b.i.d. and Yes; and > 5mg b.i.d. and No) based on the following considerations:

- LCI699 dose at week 24 (≤ 5mg b.i.d. vs. > 5mg b.i.d.): Based on the data from the PoC study, 5mg b.i.d. is estimated to be the median LCI dose at week 24 for this phase 3 trial.
- History of pituitary irradiation (Yes/No): Although supportive data is not available, it is assumed that approximately 20% of randomized patients will have a history of pituitary radiation.
- In the absence of data to expect otherwise, it is assumed that these two stratification factors are independent of each other.

To detect a difference of 40% in complete response rate between 70% in LCI699 arm and 30% in placebo arm (equivalent odds ratio equals 5.444), a sample size of 33 patients per arm will be considered adequate based on a two-sided Cochran-Mantel-Haenszel (CMH) test at the 0.05 level with 87% power. Assuming that 50% of enrolled patients will be eligible for randomization (mUFC ≤ ULN at the end of the 24 week open-label LCI699 study period), 132 patients need to be enrolled into the study.

## 3.2 Power consideration for analysis of key secondary objective

The analysis of the key secondary objective will be based on the 2-sided 95% confidence interval constructed using the Clopper-Pearson exact method. If the lower bound of this 95% confidence interval is ≥ 30%, the null hypothesis will be rejected and the complete response rate will be considered at least 30% after 24 weeks of treatment with LCI699.

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

Assuming a 50% complete response rate (mUFC ≤ ULN) at end of 24 weeks of LCI699 treatment, for 132 enrolled patients, there is 99.7% chance that the lower bound of 95% 2-sided CI of observed response rate (based on Clopper-Pearson Exact method) is larger than 30.0%.

# 4 Change to protocol specified analyses

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