NOVARTIS

Clinical Development

LCI699 (osilodrostat)

Protocol 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

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Table of contents

List of figures

List of tables

List of appendices

List of abbreviations

AE	Adverse Event
ACTH	Adrenocorticotropic Hormone
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
b.i.d.	*bis in diem*/twice a day
BMD	Bone Mineral Density
BMI	Body Mass Index
BIPSS	Bilateral Inferior Petrosal Sinus Sampling
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRH	Corticotropin-Releasing Hormone
CRO	Contract Research Organization
CSP	Clinical Study Protocol
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DDAVP	Desmopressin acetate
DILI	Drug Induced Liver Injury
DS&E	Drug Safety and Epidemiology
DXA	Dual-energy X-ray absorptiometry
ECG	Electrocardiogram
FAS	Full Analysis Set
GCS	Global Clinical Supply
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
ITT	Intention To Treat
IRB	Institutional Review Board
IRT	Interactive Response Technology
LDH	Lactate dehydrogenase
LFT	Liver Function Test
LLN	Lower Limit of Normal
LLOQ	Lower Limit Of Quantification
o.d.	*omnia die*/once a day
MRI	Magnetic Resonance Imaging
PAS	Pharmacokinetic Analysis Set
PoC	Proof of Concept
PPFAS	Per-Protocol Set for Full Analysis Set
PPRAS	Per-Protocol Set for Randomized Analysis Set
PHI	Protected Health Information
PT	Preferred Term
q.d.	quaque die/ once a day
q.o.d.	quaque otra die/ every other day
RAS	Randomized Analysis Set
REB	Research Ethics Board
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set

SASR	Safety Analysis Set for Randomized withdrawal period
SMR	Standardized Mortality Ratio
SRS	Stereotactic RadioSurgery
TBIL	Total Bilirubin
TdP	Torsades de Pointes
(m)UFC	(mean) Urine Free Cortisol
ULN	Upper Limit of Normal
ULOQ	Upper Limit Of Quantification
VAS	Visual Analog Scale

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient
Control drug	A study treatment used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Patient Number (Patient No.) Subject Number (Subject No.)	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Personal Data	Patient information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes patient identifier information, study information and biological samples.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason.
Treatment group	A treatment group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points.

Withdrawal of Consent	Withdrawal of consent from the study occurs only when a patient does not want to participate in the study any longer, and does not allow any further collection of personal data.

Amendment 5 (29-Jun-2018)

Amendment rationale

As of 25 June 2018, 91 patients are ongoing on the study. The study enrollment was completed on 22-Mar-2017.

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.

IRBs/IECs

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

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 4 (06-Jul-2017)

Amendment rationale

As of 22 March 2017, 137 patients have been enrolled (treated). The study enrollment has been completed.

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 phase, the study objectives and associated statistical sections have been revised to include extension phase 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.

Changes to the protocol

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

- Protocol synopsis: edited to be consistent with the changes made throughout the protocol.
- Editorial change has been made based on new Novartis terminology (Reporting Analysis Plan changed by Statistical Analysis Plan, SAP).
- Section 1.1.2, Section 2.1, Table 3-1, definition of the partial responder has been updated to be consistent throughout the protocol.
- Section 2.2, Table 3-1, Section 10.5.2.2, Section 10.5.2.4, Section 10.5.2.5, Section 10.5.2.6, Section10.5.7: updated to add the data collected during the optional extension phase into the objectives assessments.
- Section 2.7 : updated to include the possibility of neutropenia based on observed cases with LCI699.
- Section 4.1.5, Section 6.1.5: revised to update the duration of the optional extension period and end of study definition and to include the long term safety follow-up study modalities.

- Section 6.4.2, Section 6.4.2.1, Appendix 3: revised to update the QT-specific concomitant medication guidance for LCI699 limiting the list of prohibited drugs to medications with a "Known risk to cause TdP" and "Possible risk to cause TdP" instead of all drugs known to prolong QT.
- Section 7.2.2.4.6, Section 7.2.3: revised to clarify the serial sampling (PK and associated lab parameters) if LCI699 administration was interrupted prior to a planned visit.
- Figure 7-2: Clarification added.
- Table 7-8: Corrected to be in line with the visit evaluation schedule.
- Section 10: Clarification added on data collected for the primary analysis.
- Section 10.5.3.1: Clarification on analysis set and treatments groups for the overall study period.
- Section 13: Reference added.

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

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 3 (29-Mar-2016)

Amendment rationale

Study status: As of 01 March 2016, 75 patients have been enrolled (treated).

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 phase until the last patient completes the core period or discontinued early from core period. 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.

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.

- Section 1.1.2 : clarification to current treatment modalities included
- Section 1.2.1: additional details added to the overview of LCI699
- Section 1.2.1.2.4: added the cardiac repolarization (QT/QTc) data of LCI699 in healthy volunteers.
- Section 2.2, Section 4.3, Table 7-4, Table 7-7, Table 7-8 and Table 7-16 updated to include the changes due to the increase in duration of the optional extension period.
- Section 2.7: added a summary of the benefit-risk assessment of LCI699 specific to this study.
- Section 4.1.1, Section 4.1.2, Section 4.1.3.5, Section 4.1.3.6, Section 4.1.3.7, Section 4.1.4, Section 6.1, Section 6.1.1, Section 6.6, and Table 6-3: Added a description of the dose dispensation process, guidance on dose adjustments, recommendation for a patient dose instruction card and site communication with the patient between scheduled visits.
- Section 5.3: exclusion criteria # 16 updated to exclude patients with serum total bilirubin > 1.5 x ULN
- Section 6.1.5: updated to include the change in duration of the optional extension period and the study.
- Table 6-1: explained when emergency un-blinding may be considered
- Table 6-2: added to provide guidance for monitoring liver function and criteria for interruption and re-initiation of LCI699 for abnormal liver function.
- Section 6.5.3: added to provide guidance for follow-up on potential drug-induced liver injury cases.
- Section 6.5.3: added that Novartis DSM are unblinded in the study
- Table 7-1: explained EOT titration visit is Visit number 775, updated to specify samples to be collected in patients in China undergoing extensive PK.

- Table 7-2, Table 7-3, Table 7-4, Section 7.1.4, Section 7.1.7, Table 7-9, Section 8.1.1 and Section 8.2.2: Safety follow-up updated to 30 days after the last dose of study treatment.
- Table 7-2: updated to specify samples to be collected in patients in China undergoing extensive PK.
- Table 7-3: updated to specify samples to be collected in patients in China undergoing extensive PK and to correct inconsistency.
- Table 7-5: added to include visit schedule for year 2 and 3 of the optional extension period.
- Section 7.1.1: Clarified that consideration can be given to switching to medications with shorter washout during screening.
- Section 7.1.3: Clarified that dose is usually stable during study period 2 and dose adjustments may be needed based on mUFC and for safety.
- Section 7.1.4: Added exceptions when EOT pituitary MRI (or CT) and DXA scans are not needed.
- Section 7.1.5: added hepatic safety related discontinuation criteria, modified pituitary tumor growth related criteria.
- Section 7.2.2.4.6: updated to specify additional samples being collected and explain the samples and collection times for the samples to be collected in patients in China undergoing extensive PK.
- Section 8.1.1: additional instructions regarding AE reporting provided.
- Section 8.1.3: added definition of adverse events of special interest
- Section 8.1.3.1: added results of the thorough QT/QTc study (LCI699C2105) data of LCI699 in healthy volunteers and removed preliminary clinical data
- Section 10.1.3: provided more details about the safety analysis
- Section 10.1.4: provided more details about the Per-Protocol Set for Randomized Analysis Set and Per-Protocol Set for Full Analysis Set.
- Section 10.2, Section 10.3, Section 10.5.3.2 and Section 10.5.3.3: provided more details about the data that will be summarized.
- Section 10.5.3.1: provided more details about the treatment groups in the study
- Appendix 2: was updated to remove the corticosteroids (budesonide, fluticasone) as use of glucocorticoids is prohibited except under certain conditions as specified in Section 6.4.2.

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

The changes described in this amended protocol require IRB/IEC approval prior to implementation. The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 2 (11-Mar-2015)

Amendment rationale

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; 22-week interim analysis) and results of a 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: Corrected in the protocol, randomization is managed via an IRT system and the pharmacist, the bioanalyst and the pharmacokineticist will be blinded in the study.
- Inclusion criteria:
  - Based on the more rapid action of stereotactic radiosurgery compared to conventional radiation, the minimum period of elapsed time since the last stereotactic radiosurgery was decreased from 3 years to 2 years.
  - Rescreening is introduced in order to accommodate the long washout periods required for some cortisol-lowering medical therapies at the time of enrollment.
- Exclusion criteria:
  - QTcF exclusion limits are tightened from >470 ms to >450 ms for males, and >460 ms for females in accordance with Novartis Clinical Safety Standard Guideline.
  - Definitions for post-menopausal status and woman not of childbearing potential are added for clarity.
  - 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 broadened to include patients at high risk from macroadenomas within 2 mm of the optic chiasm.
  - Euthyroid status is based on investigator's judgment in addition to biochemical data.
  - [redacted]
  - Based on a re-evaluation of the safety monitoring schedule, certain hormone assessments have been reduced in frequency (serum 11-deoxycortisol, serum aldosterone, [redacted], and serum 11-deoxycorticosterone) or removed (urine aldosterone and urine 11-deoxycorticosterone), while other hormone assessments have been added (adrenal sex steroids: androstenedione, DHEAS, and estrone).

- The collection of specific information on the most recent medical therapy for hypercortisolism has been added to the screening assessment.
- Additional concomitant medications are now permitted, under certain conditions, including: spironolactone, eplerenone, cyproterone acetate or finasteride.
- Discontinuation criteria clarified to distinguish "confirmed" laboratory abnormalities from "confirmed and persistent laboratory abnormalities"; with the hypokalemia parameter relaxed.
- Central reading of photographs has been removed, as it is not essential for the study.
- 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 in patients with Cushing's disease (LCI699C2201, 22-week interim analysis).
- The QT monitoring section is clarified and the threshold for collecting triplicate ECG tracings is modified to include both > 500 msec and > 480 msec.
- Updated standard Novartis Discontinuation of Clinical Trial Protocol Elements language has been implemented in relevant parts of the protocol.

In addition, editorial changes and clarifications were made at various places in the protocol.

As of 02 March 2015, 16 patients have provided written informed consent for the study and 12 patients have received LCI699.

Changes to the protocol

Protocol synopsis: Edited to be consistent with the changes made throughout the protocol.

Section 1.1.2: Additional information provided on the radiation modalities for the treatment options in Cushing's disease. In addition, text was added in line with the reference (Assie et al 2007).

Sections 1.2.1.1, 1.2.1.2, 6.4.1, 6.4.2.2, Appendices 2 and 3: Revised in line with the availability of results from a clinical drug-drug interaction study [LCI699C2102]. Appendix 2 and 3 were merged.

Sections 1.2.1.2.2 and 1.2.1.2.3.3: Safety data moved from Section 1.2.1.2.2 to 1.2.1.2.3.3 and revised in line with available recent LCI699 clinical trial results information (longer-term safety and efficacy data [LCI699C2201, 22-week interim analysis].

Section 2.2: Additional information was added to explain how 24-hour UFC results reliability is ensured. In addition, the following example "following accumulation of precursors and/or ACTH" was removed since it was misleading.

Section 2.6: In line with the information added in Section 1.1.2. on the radiation modalities, the language has been updated.

[redacted]

[redacted]

Sections 4.1.1, 4.1.2 and 7.2.1.1.: Revised to provide clarity on the study conduct.

Sections 4.1.3.1, 6.1.1.1 and 6.5.3.: Corrected since patients, investigators, site personnel and the Novartis team will remain blinded until the time of treatment unblinding.

Sections 4.4, 6.1.5., 7.1.4, 7.1.5., 7.1.6, 7.1.7., 7.1.8 and the List of Abbreviations: Revised to implement the Novartis Discontinuation of Clinical Trial Protocol Elements language.

Section 5.2: The following inclusion criteria have been updated:

- 3a. Revised for clarity.
- 7: Revised in line with the added information in Section 1.1.2. on the radiation modalities.
- 8: Revised to add clarity, make updates and add information on rescreening, information also added in Section 7.1.1.

Section 5.3: The following exclusion criteria have been updated:

- 4. Updated in line with Novartis Clinical Safety Standard Guideline and for clarity.
- 6. Updated in line with Novartis Guideline on the Prevention of Pregnancies in Participants in Clinical Trials and for clarity since due to the disease a patient might qualify, patient who has had bilateral oophorectomy (making pregnancy impossible) but does not have a high FSH due to the hypercortisolemia.
- 7. Criterion no longer applicable since male contraception is no longer required in patients treated with LCI699, decision made by Novartis Medical Safety Review Board based on a thorough review of the mechanism of action of LCI699 and re-evaluation of pre-clinical and clinical data.
- 8. Updated to include not only patients with ongoing compression of the optic chiasm, but also patients at high risk from this complication, which may require emergency surgery. High risk patients are those with a macroadenoma within 2 mm of the optic chiasm. The rationale is that LCI699 therapy may increase the risk of corticotroph tumor progression and thereby increase the risk of optic chiasm compression.
- 14. Updated since euthyroid status should be assessed not only on the basis of laboratory results but also on clinical judgment.

Section 6.1.1.: Revised to provide clarity on the dosing regimen and add information on adrenal insufficiency for guidance.

Section 6.3: Revised to provide clarity on dose modifications, add information on adrenal insufficiency and on medications to treat suspected toxicities for guidance.

Section 6.4.: Corrected since there is no patient replacement policy in the study.

Section 6.4.1: Revised to provide additional information.

Sections 6.4.2.1.: As a result of one reported suspected serious adverse reaction in the clinical study LCI699C2201 of Electrocardiogram QT prolongation; the term “potential risk” has been replaced with the term “risk”. The link to the list of medications that have a known risk for causing QT prolongation has also been updated.

Section 7.1.: Revised to add rescreening information.

Section 7.1.1.3: Revised to add an assessment currently being captured in the CRF and for the most recent prior medical therapy for Cushing Disease to be captured.

Section 7.1.5: Discontinuation criteria revised to distinguish confirmed laboratory abnormalities and confirmed and persistent laboratory abnormalities.

Section 7.2.1.2: Central readings of the photographic assessments have been removed for operational reasons.

Section 7.2.1.3: Editorial changes made.

Section 7.2.1.4: Revised for clarity and to be in line with what is currently being captured in the CRF.

Section 7.1.1.4: Revised to add an assessment currently being captured in the CRF.

Section 7.2.2.4.: The following changes were made:

- Revised for clarity.
- Assessments removed for operational reasons.
- LH and FSH information moved from the thyroid panel to additional hormones sections.
- Serum Androstenedione, DHEAS, Estrone added to better characterize the change in adrenal sex steroids.
- [redacted]
- For the subset of patients participating in extensive PK assessment as well as Chinese patients, additional serum cortisol and salivary cortisol samples in correspondence to PK assessment times will be collected to allow for robust exposure-response analysis for LCI699.

Section 7.2.2.5: Revised to add clarity.

Section 7.2.2.5.6: Revised to add clarity.

Section 7.2.2.7: Revised in line with Novartis Clinical Safety Standard Guideline.

Tables 7-1, 7-2 and 7-3: Revised Visit Evaluation Schedule in line with the changes made in Sections 7.1.1.3, 7.1.1.4 and 7.2.2.4.

Section 7.2.3 and 10.5.4.: Revised to add local, country-specific intensive PK sampling for China to investigate potential ethnic differences in LCI699 pharmacokinetics at steady-state and at doses used in the treatment of patients with Cushing's disease.

Section 8.1.1.: Text removed since added incorrectly.

Section 8.1.3: Updated for clarity and remove the list of Adverse Events of Special Interest since it is not exhaustive.

Sections 3.0, 7.2.2.4, 8.1.1., 10.5.3.2, 10.5.3 and Appendix 1: Latest version of the Common Terminology Criteria for Adverse Events updated.

Section 8.1.3.1.: As a result of one reported suspected serious adverse reaction in the clinical study LCI699C2201 of Electrocardiogram QT prolongation; the term “potential risk” has been replaced with the term “risk”. Additional data added to the preliminary clinical data for clarity.

Section 8.3.: Text removed since added incorrectly.

Section 8.7.and 10.7.: Revised to clarify the Steering Committee role as to ensure transparent management of the study and not also data review.

Sections 9.3 and 9.4: Revised to be in line with changes made in Sections 7.2.1.2 and 7.2.2.4.

Section 10.1.4: Updated to clarify the definition.

Section 10.5.1.: Editorial change made.

Section 10.5.2.1, 10.5.2.3, 10.5.2.4., 10.5.2.5 and 10.6.1.: Revised to clarify how the analysis will be performed.

Section 10.5.4.: Revised to clarify how the tumor volume will be evaluated.

Section 13: References added.

Appendix 3: The link to the list of QT drugs that prolong QT has been updated. 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.

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The changes described in this amended protocol require IRB/IEC approval prior to implementation.

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Amendment 1 (15-Jul-2014)

Amendment rationale

The purpose of this protocol amendment is to address requests from the Voluntary Harmonization Procedure (VHP) review. The VHP review required that changes to the protocol be implemented to address the findings.

- In order to study efficacy and long term safety in this trial, a specified length of treatment must be defined. As a result of this finding, the definition of the optional extension period was revised.
- One of the secondary objectives is to address escape. The time-to-escape definition was not clear and required clarification.
- The premature patient withdrawal criteria required revision to ensure that pregnancy was identified as an absolute withdrawal criterion. Therefore, pregnancy will be 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 baseline before the first dose.
- 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.

Changes to the protocol

Section 4.1.4: Revised to define the extension period.

Section 4.1.6: Revised to clarify the assessment of Escape.

Section 7.1.4.1: Revised premature patient withdrawal criteria.

Section 7.2.2.7: Revised QTcF based withdrawal criteria.

Table 7-4: Revised Visit Evaluation Schedule.

Table 7-8: Revised ECG Collection Table.

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The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Protocol summary:

Protocol number	CLCI699C2301
Title	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
Brief title	Safety and efficacy of LCI699 for the treatment of patients with Cushing's disease
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The study aims to confirm long-term efficacy and safety of LCI699 for the treatment of patients with Cushing's disease. It is a pivotal trial intended to support the registration of LCI699 for the treatment of patients with Cushing's disease in the EU, Japan, and other countries. Promising results of a 10-week analysis proof of concept showed that all patients reached the primary endpoint (24-hour urine free cortisol [UFC] ≤ upper limit of normal [ULN] or ≥ 50% reduction in mUFC from baseline). In addition, all 12 patients had normalization of mUFC at least once during the study, and LCI699 was generally well tolerated.
Primary Objective(s) and Key Secondary Objective	Primary objective: • To compare the complete response rate at the end of the 8 weeks period of randomized withdrawal (Week 34) between patients randomized to continued LCI699 therapy vs. placebo by comparing the 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. 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) by assessing the 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.
Secondary Objectives	• To compare the time-to-last control of mUFC during the randomized withdrawal period between patients randomized to continued LCI699 therapy and placebo by assessing 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 discontinuation or completion of randomized withdrawal period, whichever is earlier. • To assess the complete (mUFC ≤ULN), partial (mUFC ≥ 50% reduction from baseline, but mUFC > ULN), and overall response (proportion of enrolled patients with mUFC ≤ ULN or at least 50% reduction from baseline) rate at Week 12, Week 24, Week 48 and at scheduled time points during the extension phase (provided adequate follow-up as specified in the SAP) and the last available assessment. • To assess the change in mUFC during the core and extension periods of the study by assessing: the actual and percentage change in mUFC from baseline to each post-baseline visit during the core and extension (provided adequate follow-up as specified in the SAP) at which UFC is collected; and the 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 discontinuation from randomized withdrawal, whichever occurs earlier. • To assess the change in cardiovascular-related parameters associated with Cushing's disease during the core and extension period (provided adequate follow-up as specified in the SAP) of the study by assessing: the actual and

	percentage change from baseline in: fasting glucose, HbA1c, fasting lipid profile, blood pressure, body weight, BMI and waist circumference; and the actual and percentage change from the randomization (Week 26) to the end of randomized withdrawal period (Week 34), or the last measurement (same individual parameters as before) available prior to discontinuation from randomized withdrawal, whichever occurs earlier. • To assess the change in Patient-Reported Outcomes (Health-Related Quality of Life) during the core and extension periods of the study by assessing: the change in standardized score of CushingQoL, Beck Depression Inventory-II, and EQ-5D-5L, from baseline to Week 24 and Week 48; the change in standardized score of CushingQoL, Beck Depression Inventory-II, and EQ-5D-5L, from the beginning of randomization (Week 26) to the end of the randomized withdrawal period (Week 34), or the last measurement prior to discontinuation from randomized withdrawal, whichever occurs earlier; and the change from baseline in standardized score of CushingQoL, Beck Depression Inventory-II, and EQ-5D-5L, from baseline to Week 72, 96 and the EOT extension • 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 phase by assessing the mean 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). • 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 by assessing the 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. • To assess the time-to-escape by assessing 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. • To assess general safety and AEs of special interest by assessing adverse events and laboratory abnormalities (using the National Cancer Institute-Common Toxicology Criteria (NCI-CTC) grading scale (version 4.03). AEs of special interest, as reported by the investigator, or by laboratory evaluation, ECG, Holter recording, and pituitary MRI. • To evaluate exposures of LCI699 in patients with Cushing's disease by measuring plasma concentrations of LCI699.
Study design	This is 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. Once eligibility (screening criteria met) has been confirmed, patients will enter the study. The study has four periods plus an optional extension period: **Period 1:** Single-arm, open-label (Week 1 to Week 12), is the individual patient dose titration period. Dose adjustments are based on the mean of three 24-hour UFC (mUFC) values as measured by the central lab. **Period 2:** (Week 13 to Week 24) is the period to assess the efficacy and safety of LCI699 at the therapeutic dose determined during dose titration period. **Period 3:** Double-blind, placebo-controlled randomized withdrawal (Week 26 to Week 34). Randomization is implemented at the Week 26 visit based on urine samples collected at Week 24. 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 placebo. Patients are stratified at randomization according to: LCI699 dose at Week 24 (≤ 5mg b.i.d. vs. > 5mg b.i.d.); and history of pituitary irradiation (yes/no).

	Period 4: Single-arm, open-label therapy (Week 35 to Week 48). At Week 35, patients continue open-label treatment until Week 48 based on mUFC result. Optional Extension Period: Patients 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. After discontinuing the study treatment, the patient will be followed for 30-day safety follow-up visit.
Population	The study population will be comprised of adult male and female patients with Cushing's disease who have persistent or recurrent hypercortisolism after primary pituitary surgery and/or irradiation, and patients with de novo Cushing's disease who are not surgical candidates for medical reasons, or refuse to undergo surgery.
Inclusion criteria	• Patients must have confirmed Cushing's disease that is persistent or recurrent as evidenced by: A. mUFC > 1.5 x ULN at screening (the mean of three 24-hour urine samples collected during screening, after completion of the washout period (if applicable), confirmed by the central laboratory and available at Day 1). B. Morning plasma ACTH above lower limit of normal. C. Confirmation of pituitary source of excess ACTH is defined by any of the following three criteria: (1) MRI confirmation of pituitary adenoma > 6 mm; OR (2) bilateral inferior petrosal sinus sampling (BIPSS) with either Corticotropin-Releasing Hormone (CRH) or Desmopressin acetate (DDAVP) stimulation for patients with a tumor ≤ 6mm. The criteria for a confirmatory BIPSS test are any of the following: • Pre-dose central to peripheral ACTH gradient > 2; • Post-dose central to peripheral ACTH gradient > 3 after either CRH or DDAVP stimulation; (3) histopathologic confirmation of an ACTH-staining adenoma in patients who have had prior pituitary surgery. • Patients with a history of prior pituitary surgery must be at least 30 days post-surgery to be eligible for inclusion in this study. • Patients that received glucocorticoid replacement therapy post-operatively must have discontinued such therapy for at least one week, or (5 half-lives), whichever is longer, prior to screening. • Patients with de novo Cushing's disease can be included only if they are not considered candidates for surgery (e.g., poor surgical candidates, surgically unapproachable tumors, patients who refuse to have surgical treatment, or surgical treatment is not available) • Patients with a history of pituitary irradiation can be included, provided that at least 2 years (stereotactic radiosurgery) have elapsed or 3 years (conventional radiation) have elapsed from the time of last radiation treatment to the time of enrollment into this study. • Patients are permitted to washout current drug therapy to meet these entry criteria if they have a known diagnosis of Cushing's disease. Rescreening can be used as needed to ensure washout is complete. The following washout periods must be completed before baseline efficacy assessments are performed: A. Steroidogenesis inhibitors (ketoconazole, metyrapone): 1 week B. Pasireotide s.c. (immediate release formulation): 1 week C. Dopamine agonists (e.g., cabergoline), or PPAR-gamma agonists (e.g., rosiglitazone, pioglitazone): 4 weeks D. Mifepristone: 4 weeks E. Pasireotide LAR: 8 weeks F. Mitotane: 6 months

Key Exclusion criteria	• Patients with risk factors for QTc prolongation or Torsades de Pointes, including:
	  • patients with a baseline QTcF > 450ms for males and QTcF > 460ms for females,
	  • personal or family history of long QT syndrome, or concomitant medications known to prolong the QT interval,
	  • hypokalemia, hypocalcaemia, or hypomagnesemia if not corrected before pre-dose Day 1.
	• Patients with compression of the optic chiasm due to a macroadenoma or patients at high risk of compression of the optic chiasm (tumor within 2 mm of optic chiasm).
	• Patients who have a known inherited syndrome as the cause for hormone over secretion (i.e. Carney Complex, McCune-Albright syndrome, MEN-1, AIP).
	• Patients with Cushing's syndrome due to ectopic ACTH secretion or ACTH-independent (adrenal) Cushing's syndrome.
	• Patients who have undergone major surgery within 1 month prior to screening.
	• Hypertensive patients with uncontrolled blood pressure defined as SBP > 180 and/or DBP > 100.
	• Diabetic patients with poorly controlled diabetes as evidenced by HbA1c > 9 %.
	• Patients who are not euthyroid as judged by the investigator.

Investigational and reference therapy	LCI699 or matching placebo in the form of film-coated tablets of 1 mg, 5 mg, 10 mg and (depending on availability) 20 mg for continuous b.i.d. oral administration
Efficacy assessments	• 24-hour urine to test for Urine Free Cortisol and creatinine. 24-hour UFC are mandated at screening, baseline, every 2 or 4 weeks depending on study period in core phase and every 12 weeks in extension phase. Three 24-hour samples at each time point.
Safety assessments	• Adverse events • Laboratory Evaluations (biochemistry, hematology, coagulation, Thyroid Panel, fasting plasma glucose, urinalysis and pregnancy test), • ECG, vital signs, physical exam and Cardiac Imaging
Other assessments	[redacted] Patient's health-related quality of life questionnaires
Data analysis	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 ≤ ULN (based on central laboratory result) at Week 34 and was not discontinued during the randomized withdrawal period of the study. 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 ≤ 0.05, 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. The key secondary objective is to assess the complete response rate (proportion of enrolled patients with mUFC ≤ ULN) 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 ≤ ULN (based on central laboratory result) at Week 24 and had no dose up-titration between Week 12 and Week 24. 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 the end of 24 weeks open label period of LCI699 treatment is ≤ 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 ≥ 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 primary analysis of the key secondary endpoint will be performed using FAS. An additional analysis will be performed using PPFAS.
Key words	Cushing disease, LCI699, Pituitary Gland, Adrenocorticotropic Hormone

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

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

Cushing's syndrome is rare: the reported incidence of either endogenous Cushing's syndrome or Cushing's disease in the U.S., European countries (Spain, Denmark, Belgium, and Iceland) and New Zealand has been estimated to be 1.2 to 2.4 cases per million persons per year (Etxabe et al 1994; Lindholm et al 2001; Daly et al 2006; Arnardottir and Sigurjonsdottir 2011; and Bolland et al 2011). In the U.S., a recent abstract (Broder et al 2013) reported an estimated incidence of approximately 7.6 cases per million persons per year. Among the studies listed above, the prevalence rates have been reported to range from 19 to 79 cases per million inhabitants, with the highest prevalence (79 cases per million) reported from New Zealand (Bolland et al 2011). In the US, the prevalence is less than 20,000. Cushing's disease most commonly affects adults aged 20-50 years, with a marked female preponderance.

The causes of endogenous Cushing's syndrome are classified into ACTH-dependent and ACTH-independent etiologies. The most common cause of Cushing's syndrome is Cushing's disease, which occurs in about 70% of cases, and is due to an ACTH-secreting pituitary corticotroph adenoma. The other main cause of ACTH-dependent Cushing's syndrome is ectopic ACTH secretion from non-pituitary tumors (e.g., small cell lung cancer). The ACTH-independent etiologies of Cushing's syndrome are adrenal diseases such as adrenal tumors (adenomas or carcinomas) or bilateral adrenal hyperplasia.

Endogenous Cushing's syndrome is characterized by chronic hypercortisolism, which results in a variety of metabolic abnormalities and co-morbidities that collectively lead to an overall 4-fold higher mortality rate than age- and gender-matched subjects in the general population (Etxabe et al 1994; Arnaldi et al 2003). The increased cardiovascular risk is related to the following clinical manifestations of Cushing's syndrome: metabolic syndrome, insulin resistance, visceral obesity, glucose intolerance, hypertension, dyslipidemia, and hypercoagulation. Other clinical signs and symptoms of Cushing's Syndrome include: supraclavicular and dorsal fat pads; proximal muscle weakness; osteoporosis with increased risk of fractures; skin changes (wide purple striae, hirsutism, acne); impaired immune function with increased risk of infection; neuropsychiatric disorders (depression, mood changes, and cognitive impairment), hypogonadism, and menstrual disorders in women (Newell-Price et al 2006).

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

Correction of hypercortisolism in patients with Cushing's disease is expected to improve or reverse the increased morbidity and mortality associated with untreated disease. Recently published data have suggested that recovery from the co-morbidities does occur, but may be

delayed or incomplete (Valassi et al 2012; Arnaldi et al 2012). The duration and severity of chronic hypercortisolism may impact the reversibility of the co-morbidities associated with Cushing's disease (Feelders et al 2012).

However, mortality studies have consistently shown that the mortality rate is significantly impacted by the biochemical status of the disease, i.e., persistent/recurrent hypercortisolism compared to biochemical remission of the disease. A recent meta-analysis of published mortality studies (Clayton et al 2011) showed that the standardized mortality ratio (SMR) is much higher in Cushing's disease patients with persistent hypercortisolism (SMR=5.5) than those in remission (SMR=1.2).

1.1.2 Current treatment modalities

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

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

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

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

Medical therapy is an attractive option for patients with Cushing's disease who have persistent or recurrent hypercortisolism after prior surgery and/or pituitary irradiation, and for patients

with *de novo* Cushing's disease who are not candidates for pituitary surgery because of medical reasons, or because of refusal to undergo surgery.

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

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

Several other drugs have been used with or without regulatory approval for the treatment of Cushing's disease, including: ketoconazole and metyrapone (steroidogenesis inhibitors), mitotane (adrenolytic agent), and cabergoline (dopamine agonist). Use of these drugs is based on limited data. None of these drugs have been prospectively studied in multicenter randomized trials. Thus, neither the efficacy nor the safety profiles of these medications can be considered established in the Cushing's disease population.

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

1.1.3 Unmet medical need

Cushing's disease is rare and associated with multiple co-morbidities that increase the risk of cardiovascular disease and mortality. Currently available modalities of therapy include pituitary surgery, pituitary irradiation, medical therapy and bilateral adrenalectomy. Although currently available therapies address the needs of most patients, there remain patients that have persistent or recurrent hypercortisolism and/or unacceptable toxicities.

With regard to medical therapies, the recent approvals of pasireotide and mifepristone represent major advancements. However, there is still much room for improvement beyond the existing medical therapies, because substantial subsets of patients in the target population either do not achieve normalization of mUFC or do not have the co-morbidity profile in the approved indication that would make them eligible for treatment.

Therefore there is an unmet medical need to develop new drugs with improved safety and efficacy. Based on the preliminary data from a proof-of-concept (PoC) study in patients with Cushing's disease, LCI699 shows promise in fulfilling this unmet medical need.

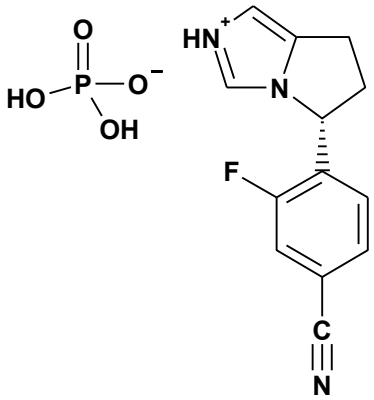
1.2 Introduction to investigational treatment(s) and other study treatment(s)

LCI699 is a potent, oral inhibitor of 11β-hydroxylase (CYP11B1), the enzyme that catalyzes the last step in the biosynthesis of cortisol. This provides the rationale for investigating the use of LCI699 in endogenous causes of Cushing's syndrome. The current development activity of LCI699 is focused on the treatment of patients with Cushing's disease (hypercortisolism due to a pituitary corticotroph adenoma), because it is the most common cause and it is relatively homogeneous. This drug also inhibits aldosterone synthase (CYP11B2), and therefore is a dual inhibitor of both cortisol and aldosterone synthesis.

1.2.1 Overview of LCI699

LCI699 is a new chemical entity with the chemical structure 4-[(5R)-6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-5-yl]-3-fluorobenzonitrile phosphate. The structural formula is shown below in Figure 1-1:

Figure 1-1 Structural formula of LCI699

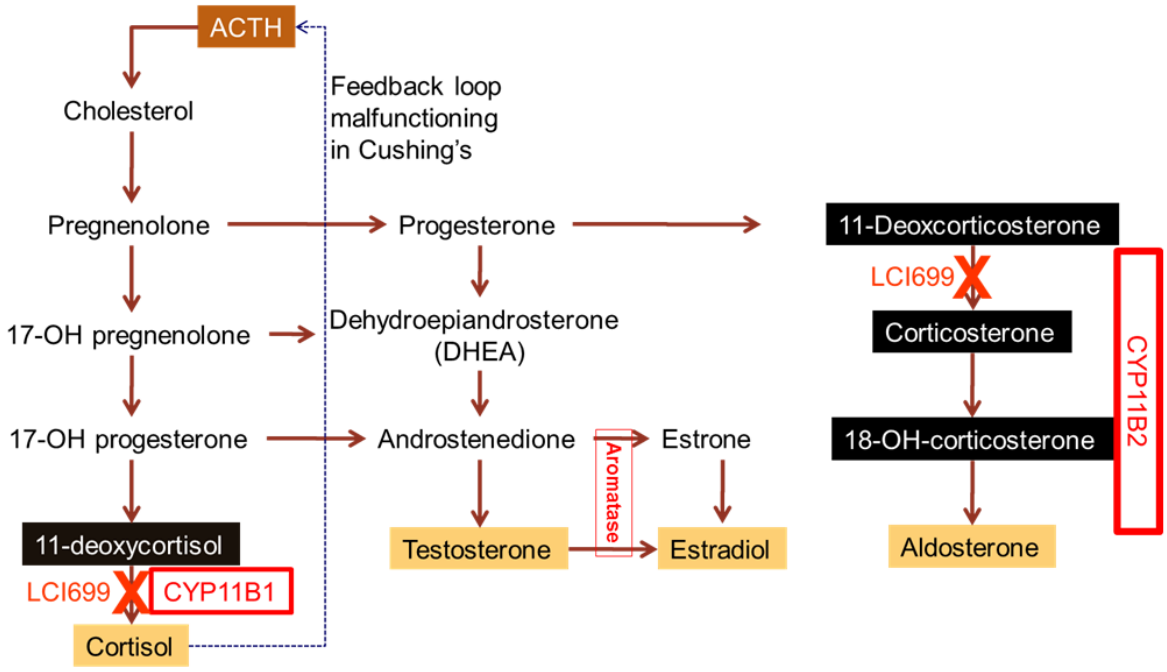


LCI699 is a potent, orally-administered dual inhibitor of 11 β-hydroxylase (CYP11B1) and aldosterone synthase (CYP11B2) in the adrenal cortex. It is manufactured as a phosphate salt and available in film-coated tablets of 1 mg, 5 mg, 10 mg and 20 mg, with matching placebo tablets, for this phase 3 study. This compound was initially developed for hypertension and primary hyperaldosteronism. At doses >3mg daily, dose-dependent impairment in the cortisol response to ACTH, and a marked decrease in the circadian rhythm of cortisol was observed. These findings raised concern of the potential for clinically significant hypocortisolism or adrenal insufficiency, and therefore the development in these indications was halted. Phase 2 studies were completed in more than 500 hypertension patients. Given the mechanism of action to inhibit cortisol synthesis at the adrenal glands, LCI699 has therapeutic potential in all forms of endogenous Cushing's syndrome (e.g., ACTH-dependent causes such as Cushing's disease due to a pituitary adenoma, and ectopic ACTH syndrome, which is associated with a benign or

malignant tumor. ACTH-independent causes include adrenal tumors (benign and malignant), and bilateral adrenal hyperplasias of various causes.

The compound is currently being developed for the treatment of patients with Cushing's disease. Higher doses of LCI699 (currently up to 30 mg b.i.d.) are being investigated for the endocrine indication relative to those used for the cardiovascular indication (up to 1 mg b.i.d). The mechanism of action of LCI699 is depicted in Figure 1-2 below.

Figure 1-2 Mechanism of action of LCI699 in Cushing's Disease



1.2.1.1 Non-clinical experience

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

1.2.1.1.1 Non-clinical pharmacokinetics and metabolism

LCI699 has been tested pre-clinically in a number of *in vitro* and *in vivo* mechanistic models. LCI699 inhibited human recombinant CYP11B1 (11 β-hydroxylase, the last enzyme in the glucocorticoid synthesis pathway) *in vitro* with an IC50 = 2.5 nM. Other effects of LCI699 include dose dependent inhibition of recombinant human aldosterone synthase CYP11B2 (IC50 = 0.7 ± 0.03 nM) and human aromatase *in vitro*, albeit at a much higher concentration with IC50 = 1.7 µM.

In vivo pharmacokinetics (PK) and toxicokinetics have been evaluated in rat and dog. LCI699 displayed high permeability in Caco-2 cells and was not a substrate for efflux mechanisms. In rats, absorption was rapid and complete with complete bioavailability indicating a minimal first-pass effect. The plasma half-life of LCI699 in rat and dog was short (~ 2 h). Exposure was dose-

proportional within the dose range investigated in the rat but over-proportional in dogs and mice. No accumulation or gender differences were observed in either species.

Protein binding was low (26.6–36.4%) with no significant species differences. Regardless of the dosing route (i.v. or p.o.), the rat and dog ADME studies indicated that elimination is mainly through metabolism and excretion in urine (~79% in rats and ~90% in dogs; unchanged LCI699 ~ 5-10% in urine and < 3% in feces). Based on *in vitro* CYP P450 inhibition profile and predicted steady state maximum concentration of 1.26 µM at 30 mg twice daily in humans, there is potential of drug-drug interaction for LCI699 with CYP1A2, CYP2C19, CYP2D6, CYP3A4/5, and CYP2E1. Results from a clinical drug-drug interaction study [LCI699C2102] are summarized in Section 1.2.1.2.1. It is unlikely for LCI699 to increase in the systemic exposure of co-medications whose clearance is mediated by P-gp, BCRP, OAT1, OAT3, OCT1, and OCT2 transport activity.

1.2.1.1.2 Preclinical safety

Safety pharmacology:

In safety pharmacology studies, proarrhythmic indices and QTc interval prolongation were observed in *in vitro* study in isolated rabbit heart and *in vivo* studies in dog and monkey with LCI699. Proarrhythmic indices were observed at 10 µM in isolated rabbit heart assay. QTc interval prolongation was noted at 50 mg/kg after 2 weeks of intravenous dosing in dogs, at 30 mg/kg oral (gavage) after single dose, and at 10 mg/kg/day in a two week study in monkeys. The preclinical data show consistency across *in vitro* and *in vivo* studies, including a monkey telemetry study. Based on the monkey telemetry data, it appears that the observed QTc effects occurred at or above 16 times the exposure of the planned maximum clinical dose of 30mg b.i.d. in healthy volunteers.

Toxicology:

In single dose toxicity study in mice, no acute toxicity was observed in mice following administration of oral doses up to 125 mg/kg, and mortality was observed at the dose of 150 mg/kg.

In repeated dose general toxicity studies up to 26-weeks in duration in the rat, and up to 39 – weeks in the dog, the main target organs were central nervous system (CNS), liver, female reproductive organs, and adrenal gland. Reversible CNS effects were seen at very high doses in dogs (≥10 mg/kg) and mice (doses ≥ 30 mg/kg). Hepatocellular hypertrophy and vacuolation were seen in 13-week and 26-week rat studies at doses ≥ 5 mg/kg and in a 13-week study in mice at doses ≥ 10 mg/kg (partially reversible). In female dogs, transient increases in ALT and AST were observed at week 5 during the 13-week study at 0.1 and 10 mg/kg. Effects on female reproductive organs (ovary, uterus and vagina) were seen in rats at doses ≥ 5 mg/kg (reversible) and in mice at doses ≥ 30 mg/kg. Male reproductive organ changes were limited to a decrease in prostate weights (no microscopic correlate) in the 26-week rat study at 20 mg/kg. No effects on female or male reproductive organs were found in dogs. In the adrenal cortex, morphological alterations were observed in dogs (zona glomerulosa) and at much higher exposure in rats (zona fasciculata/glomerulosa). They may be a result of the inhibition of adrenocortical steroid biosynthesis leading to an adaptive induction of the aldosterone/cortisol synthase pathway. In

the chronic toxicity studies, the NOAEL was 2 mg/kg in the rat (26-week), and was 10 mg/kg in the dog (39-week).

In genetic toxicology studies, no evidence of mutagenic activity was observed in the Ames test, and no evidence of chromosomal damage in the in vitro micronucleus test. Clastogenic effects at high concentrations with and without metabolic activation were reported in cultured human peripheral blood lymphocytes. In vivo genotoxicity tests in rats (micronucleus test and comet assay) were clearly negative and it is therefore concluded that LCI699 has no relevant genotoxic potential in humans.

In reprotoxicity studies (EFD in rats and rabbits, FEED study in rats), embryo/fetal toxicity was observed at doses that produced maternal toxicity in the rat and the rabbit, and increased incidence of fetal malformation was observed in rats (only occurred at the maternally toxic dose).

1.2.1.2 Clinical experience

1.2.1.2.1 Summary of clinical pharmacokinetics

The pharmacokinetics of LCI699 has been studied in healthy volunteers, patients with hypertension, and patients with hyperaldosteronism, as well as in an ongoing proof-of-concept study in Cushing's disease patients. For detailed information, please refer to the [Investigator's Brochure].

Following single oral doses of 0.5 mg to 200 mg to healthy volunteers under fasting conditions, LCI699 was rapidly absorbed with a Tmax of approximately 1 hour, consistent at all doses studied. The elimination half-life of LCI699 was 3-5 hours across all doses examined. About 6% of the dose is excreted unchanged in the urine. The pharmacokinetics of LCI699 were over-dose proportional in the dose range of 0.5 to 200 mg (single dose); for a 2-fold increase in dose, the AUC increase would be about 2.4-fold, and Cmax increase would be 2.1-to 2.4-fold [LCI699A2101].

Due to its short elimination half-life, LCI699 does not accumulate in plasma following twice-daily multiple dosing up to 3 mg b.i.d., and there is no change in the kinetics on repeated dosing. Accumulation ratio based on AUC (Day 1 vs. Day 14) is 0.8 - 1.3 in subjects dosed with ≤3 mg b.i.d. Typically, the coefficient of variation for plasma LCI699 AUC is in the region of 11 – 40% in healthy subjects after an oral dose [LCI699A2101].

For exploratory assessment of food effect, pharmacokinetics of a single oral dose of 100 mg LCI699 under fasting conditions was compared with that following a high fat meal in the first-in-human study (n=3 – 5). Administration of 100 mg LCI699 with a high fat meal resulted in a reduction in AUC and Cmax by 14% and 25%, respectively, and the median Tmax was delayed from 1 h to 2.5 h after high fat meal. The impact is not considered clinically significant; the delay in Tmax and impact on Cmax is expected as food delays gastric emptying and prolongs intestinal transit time.

Impact of ethnic origin on LCI699 pharmacokinetics was investigated in Caucasian and Japanese healthy male subjects following single and multiple doses of LCI699 (0.25, 0.5, 1, 2 mg). LCI699 exposure (AUC) was 18%, 44%, and 66% higher in Japanese healthy volunteers in comparison to Caucasians after single dose of 0.5 mg, 1 mg and 2 mg LCI699, respectively,

and a larger difference is observed at higher doses. Body weight difference (mean body weight: 64.6 to 68.6 kg for Japanese vs. 70.7 to 77.6 kg for Caucasians) was not shown to be a major determinant of the race effect on exposure [LCI699A2102].

Results from the human ADME study indicate that the majority of the [^{14}C]-LCI699 radioactivity 50 mg dose was eliminated in the urine (mean: 90.6%) with only a minor amount eliminated in the feces (mean: 1.58%). The percentage of the dose eliminated in the urine as unchanged LCI699 was also minor (mean: 5.19%). Thus, metabolism was found to be the major clearance pathway for LCI699 in humans with renal clearance making only a minor contribution. Metabolism of LCI699 was extensive in humans via multiple pathways (and combination of pathways). The primary metabolic reactions observed in this study included direct glucuronidation, hydroxylation of the pyrrolidine-ring system, oxidation and degradation of the imidazole ring, N-methylation, and ribose conjugation. The most abundant circulating metabolite was M34.5, which was formed via di-oxygenation of the imidazole ring of LCI699. There is no single metabolic pathway that contributes significantly to the overall elimination of LCI699 [LCI699C2101].

Results from a cocktail drug-drug interaction study [LCI699C2102] showed that LCI699 is a weak inhibitor for CYP3A4/5 and CYP2D6 (increased AUCs of midazolam and dextromethorphan ~1.5-fold), and a moderate inhibitor for CYP1A2 and CYP2C19 (increased AUC of caffeine and omeprazole ~2.5- and ~1.9-fold, respectively).

Assessment of LCI699 PK is ongoing in Cushing's disease patients. Trough concentrations were available for 10 patients from the interim analysis after 10 weeks of LCI699 treatment, and ranged from 0.336 ng/mL (after 2 mg b.i.d) to 204 ng/mL (after 50 mg b.i.d). The median (range) of trough plasma LCI699 concentrations at the time when mUFC was normalized, or reduced by at least 50%, was 5.0 (0.3 – 49.3) ng/mL (n=10). [LCI699C2201 Interim CSR].

1.2.1.2.2 Results of LCI699C2201study in Cushing's disease

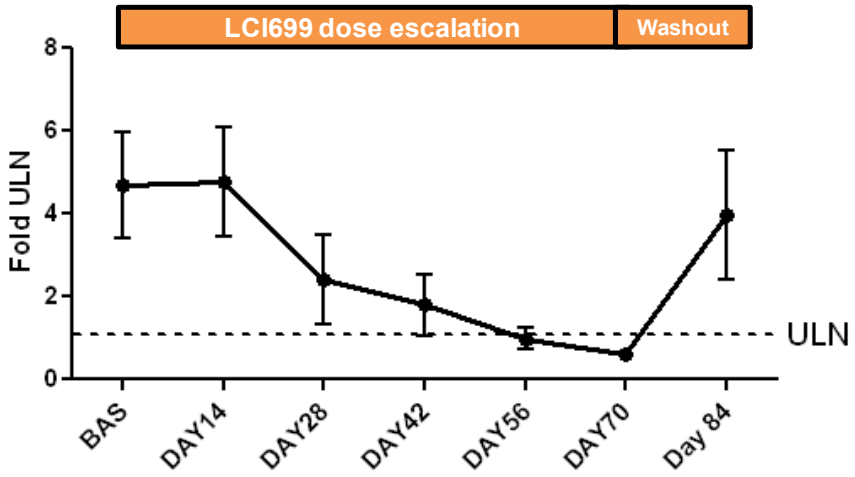
The purpose of the LCI699C2201 study was to determine whether the ability of LCI699 to inhibit 11β-hydroxylase could safely reduce urinary free cortisol (UFC) in patients with Cushing's disease. This was initially studied over a 10-week treatment duration Proof-of Concept (Part I). Part II of the study aimed to further evaluate the observations from the Part I by enrolling a cohort of patients who participated in Part I (Follow-up cohort) and a new cohort (Expansion cohort) of patients and to evaluate the longer-term efficacy and safety of LCI699 treatment for a total duration of 22 weeks; results of the longer-term efficacy and safety of LCI699 are also available.

In Part I, LCI699 was effective in controlling cortisol production in all 12 patients studied. At daily LCI699 doses between 2 mg b.i.d. and 50 mg bid, 24-hour mUFC decreased rapidly and normalized at least once in all patients studied. Individual patient mUFC reduction over time and dose-response is depicted in [redacted]. In general at 5 mg b.i.d. patients showed mUFC reduction after 2 weeks (at first mUFC measurement after dose titration).

The primary endpoint, defined as mUFC ≤ ULN or ≥ 50% decrease from baseline at day 70, was achieved by all patients. Overall, the mean time to response (UFC normalization or ≥ 50% reduction from baseline) was 34.3±14.1 days. The mean daily dose (± SD) of LCI699 required to reach the primary endpoint was 13.5±13.9 mg b.i.d. with 75% of patients normalizing mUFC

on ≤ 10mg b.i.d. At Day 84, two weeks after LCI699 was withdrawn, mUFC levels increased to a mean of 4-fold above upper limit of normal (ULN) (Figure 1-4).

Figure 1-4 Arithmetic mean and SE plots for fold ULN of mUFC (PD analysis set)

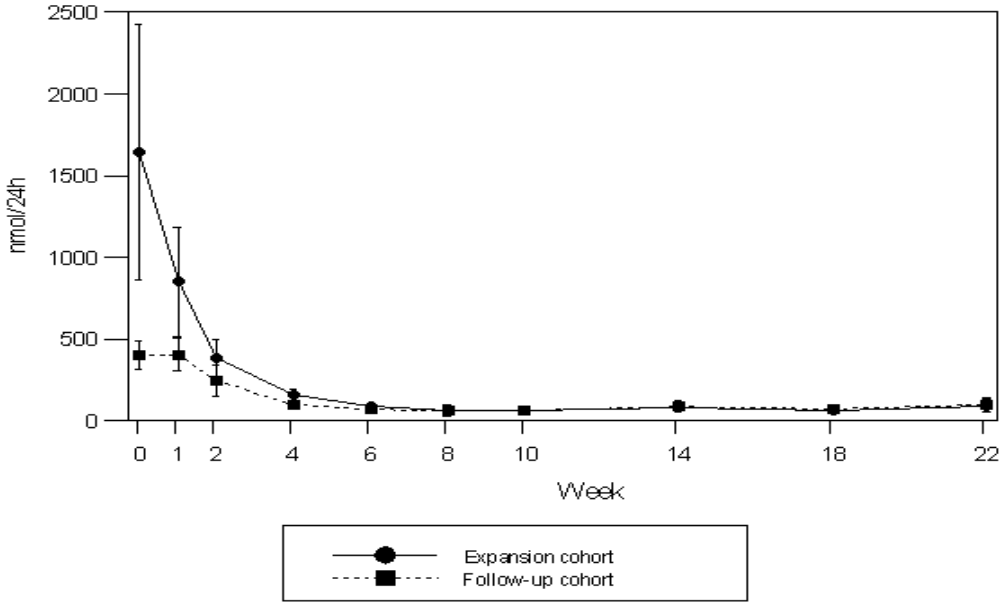


Source: In-text Figure 11-2, 10-week interim CSR study [LCI699C2201].

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

In Part II, 17 out of 19 patients completed the 22 weeks treatment period and 15 of 19 (79%) had normal mUFC levels at week 22. During treatment with LCI699, the mean mUFC levels decreased quickly and stabilized to a normal level (11 to 138 nmol/24h) at Week 4 (Figure 1-5). After Week 4, normal mean mUFC levels were observed through the study up to Week 22. All patients attained UFC normalization at least once during the study, and no patient “escaped” UFC control.

Figure 1-5 Mean (+/-SE) mUFC (nmol/24h) over time by cohort



1.2.1.2.3 Overview of LCI699 clinical safety

Clinical safety data with LCI699 has been obtained from seven completed studies and one ongoing study. A total of approximately 954 subjects participated in these studies. Of these, a total of 683 were treated with LCI699: 131 healthy male volunteers, 516 patients with hypertension, and 27 patients with Cushing's disease.

In the clinical trials for the treatment of hypertension or primary hyperaldosteronism, LCI699 was tolerated with the overall incidence of adverse events being similar to placebo. AEs were generally of mild to moderate intensity. Both SAEs and discontinuations due to AE were infrequent, and were reported at a rate similar to placebo in the hypertension studies. The most common AEs across these studies were: headache, dizziness (including postural dizziness), nausea, diarrhea and fatigue. There were also AEs of hyperkalemia and impaired ACTH-stimulated cortisol response in these trials, which are consistent with the potential for hypocortisolism and hypoaldosteronism.

In Part I of the study [LCI699C2201], all 12 patients (100%) experienced adverse events but these were generally mild to moderate in severity (NCI CTC grade 1 or grade 2). Fatigue, muscle cramps, dizziness and gastrointestinal events were the most common events suspected to be drug related. Four patients reported AEs consistent with cortisol and/or aldosterone withdrawal; dose reductions or temporary dose interruption in these patients improved the symptoms. There were no discontinuations related to study drug and no serious adverse events of suspected drug relationship.

In Part II of study LCI699C2201, LCI699 was generally well tolerated. Except for one patient in the Expansion cohort, all patients experienced AEs, grade 1/2 in most of the cases. Adrenal insufficiency, nausea, fatigue and increased levels of oxycorticosteroids, blood corticotrophin, blood testosterone in females were the most common AEs suspected to be drug related (by PT).

Two patients experienced a total of 3 SAEs.

One patient experienced grade 3 pituitary-dependent Cushing's syndrome (PT). The SAE resulted in hospitalization/prolonged hospitalization and was not suspected to be related to the study drug. This SAE was continuing at the time of the data cut-off date.

Another patient experienced 2 SAEs concurrently: grade 3 gastroenteritis (PT) and grade 1 Electrocardiogram QT prolongation (PT). The gastroenteritis resulted in hospitalization/prolonged hospitalization, was not suspected to be related to the study drug and resolved with concomitant medication. The Electrocardiogram QT prolongation was suspected to be related to the study drug by the investigator, but causality is not clear. There were no cardiac symptoms or arrhythmia reported. The SAE “electrocardiogram QT prolongation” was ongoing at the time of the data cut-off date.

One patient discontinued the study drug due to AEs. This patient reported (by PT) grade 3 papule, and grade 1 diarrhea, malaise, muscular weakness and nausea. All the AEs were suspected to be related to study drug and the patient discontinued the study drug after two weeks treatment.

In reviewing the clinical trial experience with LCI699 to date, AEs have been identified that are consistent with the mechanism of action of the drug as an inhibitor of both cortisol and aldosterone synthesis. These can be summarized as follows:

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

A more detailed list of potential AEs related to the mechanism of action of LCI699 can be found in Section 8.1.3, “AEs of Special Interest”. For a comprehensive review of clinical safety data with LCI699, see the [Investigator’s Brochure].

1.2.1.2.4 Study CLCI699C2105: QT/QTc data in healthy volunteers

The cardiac repolarization liability of LCI699 was assessed in the definitive ICH E14 compliant thorough QT/ QTc Study (TQT) study [CLCI699C2105] in 86 healthy male and female subjects. A maximum mean ΔΔQTcF of 25.4 ms was observed on the supratherapeutic LCI699 dose of 150 mg (5-fold higher than the maximum clinical dose of 30 mg), with absence of a relevant QT effect on the therapeutic LCI699 dose of 10 mg (ΔΔQTcF 0.3 ms; 90% CI −1.50, 2.16).). No subject experienced QTcF values >500 ms, nor increases from baseline >60 ms. The maximum effect was observed at Tmax (1 hour post-dose). No dose-related effects were observed for the cardiac intervals (QRS, PR, or HR), or on blood pressure on LCI699 10 mg or 150 mg. No new safety concerns were identified in this study.

A population-PK analysis was performed to estimate the peak exposure (Cmax) of the highest planned clinical doses of LCI699 (20 mg and 30 mg), based on the pooled PK data from the LCI699 studies A2101, C2105, and C2201 (total N=178). The predicted arithmetic mean and

geometric mean Cmax,ss of LCI699 20 mg was 174 and 168 ng/mL, and on LCI699 30 mg was 284 and 275 ng/mL, respectively. The concentration-QTcF effect model from study [LCI699C2105] was then applied to the predicted Cmax values for LCI699 20 mg and 30 mg from the Population-PK analysis. Based on the predicted exposure levels, the predicted maximum mean QTcF on LCI699 20 mg is 4.1 ms (CI 2.98, 5.28), and the predicted maximum mean QTcF on LCI699 30 mg is 6.3 ms (CI 5.13, 7.42).

The results remained below the QTcF effect of regulatory concern (i.e., an upper boundary of the 90% CI < 10 ms) and fully support the use of LCI699 doses up to 30 mg.

2 Rationale

2.1 Study rationale and purpose

LCI699 is a potent inhibitor of 11β-hydroxylase, the enzyme that catalyzes the last step in the biosynthesis of cortisol. This provides the rationale for investigating the use of LCI699 in endogenous causes of Cushing's syndrome. This drug also inhibits aldosterone synthase.

The most common cause of Cushing's syndrome is an ACTH-secreting pituitary adenoma (Cushing's disease). The effect of LCI699 in patients with recurrent or persistent hypercortisolism from Cushing's disease was investigated in the Proof-of-Concept (PoC) study [CLCI699C2201]. The results of the10-week analysis showed that all 12 patients reached the primary endpoint (24-hour urine free cortisol [UFC] ≤ upper limit of normal [ULN] or ≥ 50% reduction in mUFC from baseline). In addition, all 12 patients had normalization of mUFC at least once during the study, and LCI699 was generally well tolerated.

These promising results are now being further evaluated in an amendment to protocol [CLCI699C2201] that plans to study patients for a longer period of time (22 weeks with an optional one year extension). A total of 19 patients have been enrolled in the amended study, including 15 new patients and 4 patients that were previously enrolled.

The present Phase 3 study [CLCI699C2301] is intended to support the registration of LCI699 for the treatment of patients with Cushing's disease who have persistent or recurrent hypercortisolism after primary pituitary surgery, and patients with *de novo* Cushing's disease who are not surgical candidates for medical reasons, or refuse to undergo surgery.

2.2 Rationale for the study design

The study aims to confirm long-term efficacy and safety of LCI699. A period of individual-patient dose titration during the first 12 weeks (see Section 4.1 for details of the study design) is followed by monitoring for sustained efficacy and safety of this therapeutic dose for the second 12 weeks of the study. At week 24, the proportion of patients with normal UFC (complete responders, mUFC ≤ ULN) is assessed as the key secondary endpoint.

Patients with normal mUFC (≤ ULN) at week 24 and that meet the criteria specified in Section 4.1.3.2 are eligible to enter a double-blind, placebo-controlled, randomized withdrawal period that is designed to confirm the efficacy of LCI699 in controlling UFC relative to placebo for up to 8 weeks. At the end of randomized withdrawal, the randomized patients enter a second open-

label period of LCI699 therapy to week 48 (in the core study). Patients that were not randomized continue to be monitored for efficacy and safety on LCI699 to week 48.

Patients that plan to participate only in the core part of the study stop study drug at Week 48, and return for an end of study visit 4 weeks later, at week 52. Patients that wish to continue on to the extension part of this study are re-consented at Week 48, and continue study drug and assessments without interruption. The extension part of the study is intended to collect long-term safety and efficacy data. The optional extension period will end after the last patient completes the core period or discontinued early from core period. Patients who continue to benefit from treatment will be offered participation in a separate long-term safety follow-up study. This study design was selected for the pivotal trial of LCI699 in patients with Cushing's disease for several reasons:

- Individual dose titration is required based on the available data due to high inter-subject variability in effective dose and narrow therapeutic window (potential risk of hypocortisolism or acute adrenal insufficiency)
- Follow-up at steady dose during weeks 12-24, as well as during the second open-label period (from the end of randomized withdrawal to Week 48) aim to demonstrate long-term safety and efficacy without the need for further dose escalation due to therapeutic escape.
- The design permits dose reductions and temporary dose interruptions for safety reasons at any time during the study, but the investigator is blinded to randomized treatment assignment only if this occurs during the randomized withdrawal period
- The randomized withdrawal period provides an efficient way to demonstrate the efficacy of LCI699 vs. placebo. Efficiency of design is relevant in a rare disease, because of the difficulty in finding eligible patients. Randomized withdrawal, in this case with a rescue treatment available (see below) minimizes the duration of placebo treatment, while allowing efficacy to be demonstrated.
- It is not ethical to use a long-term placebo control, because chronic uncontrolled hypercortisolism results in increased morbidity and mortality (Clayton et al 2011).
- Randomized withdrawal provides the design elements of double-blinding, placebo control therapy for comparison, and randomized allocation to continue study drug or change to placebo.

FDA (Draft Guidance for Industry on Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products, December 2012) recommends a randomized withdrawal design for target populations with the above listed characteristics.

Some of the advantages of the proposed study design are:

- The population that undergoes randomized withdrawal is enriched by including only those patients that have responded to treatment during an open-label run-in period. This design is an efficient way to demonstrate the efficacy of a drug without requiring long-term exposure of patients to a placebo control.
- Patients who do not have a complete response may receive benefit from a partial response. Such patients are not randomized but continue to be monitored for long-term efficacy and safety until the end of the trial.

- In the case of this study, there is a procedure for managing patients with uncontrolled hypercortisolism during the 8-week randomized withdrawal. Patients with mUFC > 1.5 x ULN (with at least 2 individual UFC results > 1.5 x ULN) at any study visit during randomized withdrawal will be discontinued from this period of the study, and will resume treatment with open-label LCI699 at a dose selected by the investigator. This minimizes the duration of exposure to ineffective treatment.

Primary and secondary endpoints

One of the key treatment goals in patients with Cushing's disease is normalization of the biochemical abnormalities (Biller et al 2008). The results of the 10-week analysis in 12 patients with Cushing's disease in the proof of concept (PoC) study [CLCI699C2201] demonstrated that LCI699 is highly effective in normalizing urinary free cortisol in this population.

The clinical importance of normalizing UFC in patients with Cushing's disease is emphasized by the results of a recent meta-analysis of published mortality (Clayton et al 2011). This meta-analysis showed that the standardized mortality ratio (SMR) is much higher in Cushing's disease patients with persistent hypercortisolism (SMR=5.5) than those in remission (SMR=1.2).

The 24-hour UFC test is considered the best diagnostic test for hypercortisolism. The primary efficacy assessment in Study [CLCI699C2301] is based on the mean of three 24-hour urinary free cortisol (mUFC) collections, within a period of two weeks, at the end of 8 weeks (at Week 34) of randomized withdrawal. The primary objective is to compare the complete response rate (proportion of patients with mUFC ≤ ULN) at the end of 8 weeks of randomized withdrawal (at Week 34) between patients randomized to continued LCI699 therapy or placebo.

As 24-hour UFC is the primary efficacy assessment, special care is taken to ensure that the results are reliable. The 24-hour urine collection must be within defined upper and lower limits for urine volume and urine creatinine. These limits are intended to avoid the reporting of misleading results because of incomplete urine collections or extremes of urine concentration from undertreatment or overtreatment of central diabetes insipidus if present. In addition, patients with eGFR < 60 mL/min are excluded because reduced urine free cortisol excretion has been reported in patients with moderate or severe renal impairment (Allen Chan et al 2004; Issa et al 1999; and Sharp et al 1986). The method used for measurement of UFC at the central laboratory is liquid chromatography-tandem mass spectrometry (LC-MS/MS). In contrast to immunoassays, LC-MS/MS has the advantage of measuring cortisol accurately and exclusively, without concern of interference by cross-reactivity of accumulating cortisol precursors (e.g., 11-DOC) with LCI699 therapy (Monaghan et al 2014).

In addition to the primary endpoint, the key secondary endpoint is the complete response rate (proportion of patients with mUFC ≤ ULN) at the end of 24 weeks of dose-titration and treatment with LCI699 in the initial single-arm, open label part of this trial. This is a clinically meaningful endpoint in that it assesses the proportion of patients that have achieved fully controlled mUFC at that time point. In addition, the requirement for a normal mUFC (mUFC ≤ ULN) presents a hurdle for eligibility to enter the randomized withdrawal part of the study.

Other secondary endpoints [redacted] endpoints correspond to the secondary [redacted] objectives, respectively. Several relevant clinical endpoints are captured: the

change from baseline in fasting glucose, HbA1c, fasting lipids, blood pressure, weight, BMI, and waist circumference; the change from baseline in BMD by DXA scan at the lumbar spine and total hip; and the change from baseline, in Health Related Quality of Life, as measured by the Cushing's disease-specific QoL questionnaire (CushingQoL), the Beck Depression Inventory (BDI-II), and the general HRQoL instrument EQ-5D-5L at time points indicated in Section 3.

2.3 Rationale for dose and regimen selection

The rationale for b.i.d. dosing of LCI699 is based on its half-life of 3-5 h. This regimen was used in the PoC study [CLCI699C2201] as well. Originally modeling of PK exposure estimated that a dose of 4-5 mg b.i.d. is expected to achieve a plasma concentration above the *in vitro* IC50 for CYP11B1 (2.5 nM) for a full 24 hours for efficacy consideration; however, 2 mg b.i.d was chosen to be the starting dose in the PoC study based on safety considerations, i.e., to reduce the risks associated with potential hypocortisolism or adrenal insufficiency:

- Glucocorticoid withdrawal due to rapid correction of elevated serum cortisol,
- Biochemical hypocortisolism (UFC < LLN),
- Symptomatic hypocortisolism or adrenal insufficiency (potentially life-threatening).

There were four events of suspected hypocortisolism (glucocorticoid withdrawal) that improved with dose reduction or dose interruption during the 10-week PoC study [CLCI699C2201]. Since these events occurred during the 10-week dose titration period, they support a conservative approach to the starting dose of LCI699. In addition, since the 10-week analysis, one patient in the ongoing study [CLCI699C2201] had biochemical evidence of hypocortisolism on 2mg b.i.d., and their LCI699 dose was reduced to 1 mg b.i.d.

The 10-week analysis of the PoC study [CLCI699C2201] showed that the dose of LCI699 required for normalization of mUFC ranged from 2 mg b.i.d to 50 mg b.i.d after individual dose titration, with nearly all patients (11/12) achieving UFC normalization at > 2 mg b.i.d. Trough concentrations at mUFC normalization also varied widely, ranging from 0.3-49 ng/mL. This indicates that there is a broad range (up to 25-fold in LCI699 dose) of between-patient sensitivity to LCI699 with respect to normalization of mUFC, and there was no apparent relation between the therapeutic dose or exposure (trough concentrations) and the baseline mUFC.

Thus, it appears that individual dose titration starting at 2 mg b.i.d. is an appropriate method to assess the efficacy and safety of LCI699. Fixed-dose comparisons of LCI699 doses would carry the risk of hypocortisolism if a relatively high dose is administered to a patient that is very sensitive to LCI699; in extreme cases, such a complication could present as a potentially life-threatening adrenal crisis.

This pivotal study will therefore start with a single-arm, open-label, individual patient dose titration period during the first 12 weeks. The following dose escalation sequence will be followed: 2 mg b.i.d., 5 mg b.i.d., 10 mg b.i.d., 20 mg b.i.d., and 30 mg b.i.d. The dose of LCI699 is titrated on the basis of the mean of three 24-hour urine free cortisol (mUFC) levels that are collected every two weeks during the dose titration period. Since at least one patient (see above) in the ongoing study [CLCI699C2201] had biochemical evidence of

hypocortisolism on 2mg b.i.d., the dose can be lowered to 1mg b.i.d. if this occurs in the present study.

Please refer to Section 6.1.1 for more detailed information regarding dose adjustment.

2.4 Rationale for choice of combination drugs

Not applicable.

2.5 Rationale for choice of comparators drugs

Not applicable.

2.6 Rationale for inclusion of patients post pituitary irradiation

In this protocol, patients with a history of pituitary irradiation are eligible for enrollment, provided that at least 2 years (stereotactic radiosurgery (SRS)) have elapsed or 3 years (conventional radiation) have elapsed from the time of last radiation to the time of enrollment into this study. Such patients must have uncontrolled hypercortisolism post-radiation at the time of screening. The justification for including such patients is that the therapeutic effect of radiation is delayed, but with SRS the median onset of biochemical remission is 17 months (Sheehan et al 2013), while with conventional radiation the onset is typically within 2-3 years after treatment (Minniti et al 2007). With conventional radiation, there is a plateau with a small incremental benefit up to 10 years or longer after treatment (Losa et al 2010).

Published data show that biochemical remission is observed in 28% of patients at 1 year, 73% at 3 years, 78% at 5 years, and 84% at 10 years (Minniti et al 2007). Since the rate of decline in UFC is expected to be much slower as a result of radiation than as a result of LCI699 treatment, the potential for a confounding effect of radiation on efficacy is low.

2.7 Benefit-risk assessment of LCI699 in study population

Potential patient benefits

There is an unmet medical need in patients with Cushing's disease which is a rare and serious disease with limited options for medical therapy. A proof-of-concept study ([LCI699C2201] Part 1) in 12 patients with uncontrolled Cushing's disease showed that 11/12 patients had a normal mean UFC at the end of 10 weeks of LCI699 therapy. Continuation of the amended study ([LCI699C2201], Part II core) showed that 15/19 (79%) patients had normal mean UFC levels at the end of 22 weeks of LCI699 therapy; there was a trend toward improved fasting glucose and HbA1c in patients with diabetes at baseline, and an improved fasting lipid profile in patients with dyslipidemia at baseline. Based on these results LCI699 is a promising potential new therapy in patients with uncontrolled Cushing's disease who have failed or are unable to receive primary surgical therapy

Study-specific risks

Study-specific risks in study [LCI699C2301] include: the potential for prolonged periods of uncontrolled hypercortisolism during the screening period while prior cortisol-lowering therapy is washed out. The duration of washout ranges from 1-8 weeks for nearly all drugs, and 6 months for mitotane. For patients who begin the study on a medication that requires a washout periods

of ≥ 4 weeks, it is possible to switch to a medication with a short washout period (e.g., 1 week) until the last part of the washout. Patients randomized to the placebo arm during the randomized withdrawal period may also experience uncontrolled hypercortisolism for up to 8 weeks duration (Week 26 to Week 34); this risk is mitigated by the "rescue" procedure, in which patients with mean UFC > 1.5 x ULN (with at least 2 of the 3 individual UFC levels > 1.5 x ULN) during the randomized withdrawal period are discontinued from randomized withdrawal and changed to open-label treatment with LCI699.

Risks of LCI699 treatment in study population

Known risks of treatment with LCI699 in patients with Cushing's disease include: QT prolongation, adrenal insufficiency, AEs related to the accumulation of precursor molecules, including: increased or decreased blood pressure, hypokalemia or hyperkalemia, hyponatremia, weight gain, edema, and increase in the synthesis of sex steroids (primarily adrenal androgens in women) that may lead to menstrual changes and hirsutism in women and acne in either men or women. Skin rash has been observed. Corticotroph tumor progression, with or without compressive symptoms, is a potential risk.

In addition, treatment with LCI699 can potentially result in neutropenia, which is considered to be an indirect effect of cortisol reduction, as reported in the literature. During hormonal control, a significant decrease of neutrophil count, which is commonly elevated in patients with Cushing's disease, has been reported demonstrating the effect of glucocorticoids on these blood cells (Masri-Iraqi et al 2014). This effect has also been observed with LCI699 in the Cushing's disease trials and has included cases of neutropenia which were associated with mUFC levels that were either below normal or have had a rapid and substantial decline from baseline. In the cases observed, neutropenia has rapidly reversed with discontinuation of LCI699, and has also reversed when LCI699 was continued, typically with decreasing doses.

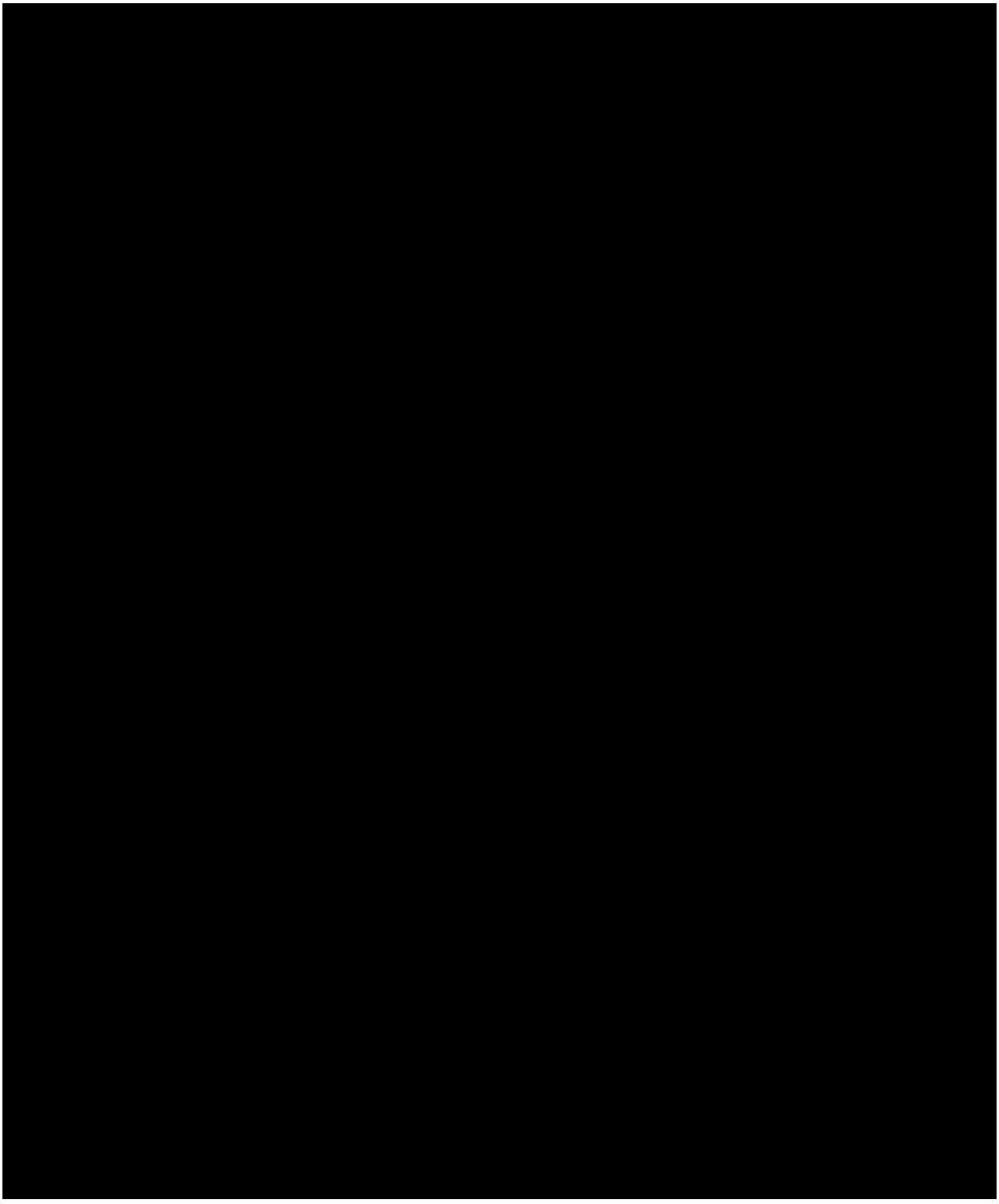
Mitigation of the potential risks related to LCI699 treatment include: frequent study visits with careful monitoring for adverse events and toxicities including those that have been observed in previous studies with LCI699: vital signs, blood chemistry including urine, serum, [redacted] cortisol levels, plasma ACTH, electrolytes, renal and liver function, fasting lipid profiles, HbA1c, sex steroid levels (testosterone, estradiol, adrenal androgens), immediate precursor levels to cortisol and aldosterone, safety ECGs at the time of Cmax, and pituitary MRI scans.

In addition, the protocol provides specific guidance for safety follow-up of possible liver toxicity (increased transaminases, increased total bilirubin) and an algorithm for monitoring and management of QT prolongation. PK sampling will be conducted in all patients to measure LCI699 plasma concentrations and assess for any correlation with adverse events or for potential drug-drug interaction.

A Steering Committee has been established; see Section 8.7 for additional detail. A Novartis Safety Management Team (SMT) exists to review and evaluate all emerging safety data for potential new safety signals on a regular basis and to evaluate safety management across the program.

Conclusion

Based on current data, and the planned risk mitigation processes, the overall benefit-risk of trial participation is expected to be positive for all trial subjects, including those randomized to placebo during the randomized withdrawal period.



3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4.
To 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.	
Key secondary		Refer to Section 10.5.1.
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.	
Other secondary		Refer to Section 10.5.2.
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.	
To assess the complete, partial, and overall response rate at Week 12, Week 24, Week 48, and at scheduled time points during the extension phase 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 phase (provided adequate follow-up as specified in the SAP), and the last available assessment Partial response rate: proportion of enrolled patients with ≥ 50% reduction from baseline in mUFC, but mUFC > ULN) at Week 12, Week 24, Week 48, and at scheduled time points during the extension phase (provided adequate follow-up as specified in the SAP), and the last available assessment. 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 phase (provided adequate follow-up as specified in the SAP), and the last available assessment.	

Objective	Endpoint	Analysis
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 as specified in the SAP) at which UFC is collected • 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 as specified in the SAP) of the study in: fasting glucose, HbA1c, fasting lipid profile, blood pressure, body weight, BMI and waist circumference • 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).	Refer to Section 10.5.2.4.
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, Beck Depression Inventory-II, and EQ-5D-5L, from baseline to Week 24 and Week 48. • Change in standardized score of CushingQoL, Beck Depression Inventory-II, and EQ-5D-5L, 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. • Change from baseline in standardized score of CushingQoL, Beck Depression Inventory-II, and EQ-5D-5L, from baseline to Week 72, 96 and the EOT extension	
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 phase.	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).	
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	
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.	

Objective	Endpoint	Analysis
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). AEs of special interest, as reported by the investigator, or by laboratory evaluation, ECG, Holter recording, and pituitary MRI.	
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	
[redacted]		

4 Study design

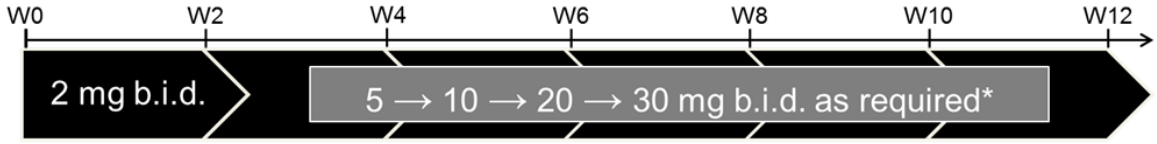
4.1 Description of study design

This is 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. The study has four periods plus an optional extension period, which are described below.

4.1.1 Study Period 1

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

Figure 4-1 Schematic of study period 1



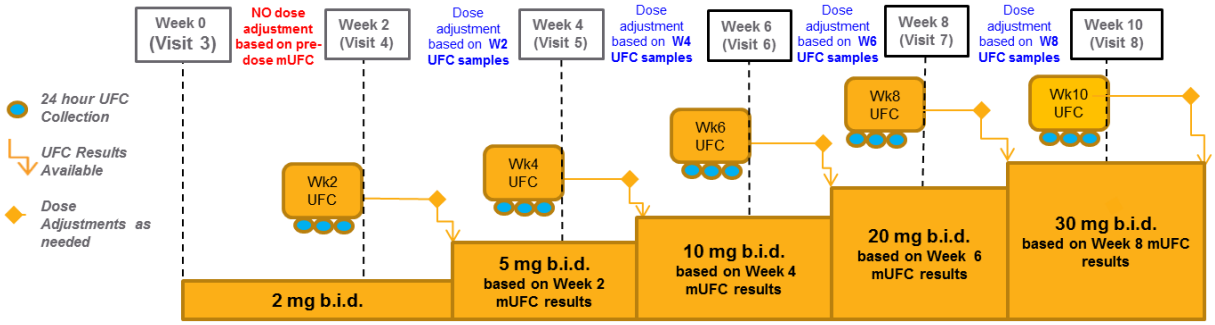
* Dose can be down titrated to 1 mg b.i.d. if needed

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 maintained if mUFC is within the normal range and the patient does not have signs or symptoms of hypocortisolism or adrenal insufficiency. The dose is reduced if mUFC < LLN, or if the patient is symptomatic and mUFC is in the lower part of the normal range. At Week 0 and Week 2, dose increase is not permitted.

If a dose adjustment is required, sites should inform patients of the dose change by phone, as soon as possible once the mUFC results are available (e.g. ideally within 24 hours), which is expected to occur in between study visits. Please refer to Section 6.1.1 for details on communication and implementation of dose changes.

To minimize the risk of dosing errors, it is **very important** that the patient receive written instructions that are clear and detailed but easy to follow at every visit. Please refer to Section 6.1.1 for details on dosing instructions at visits.

Figure 4-2 Example: Timing of study visits, UFC collection, and dose adjustments during Period 1 in a patient with dose up-titration



Study visits are at Week 0 (Day1) and Weeks 2, 4, 6, 8, 10 and 12. Once mUFC results are available and a dose adjustment is required, sites should inform patients of the dose change by phone or under direct supervision by the site during an unscheduled visit prior to the next scheduled visit.

Note:

- LCI699 dose is increased if the mean of 3 urine samples (mUFC) is **above normal (> ULN)**.
- LCI699 dose is maintained if the mUFC value is in the **normal range** and the patient does **not** have signs or symptoms of hypocortisolism or adrenal insufficiency.
- LCI699 dose is reduced if the mUFC value is **< LLN** OR the patient has signs and symptoms of **hypocortisolism or adrenal insufficiency** and the mUFC value is in the **lower part of the normal range**.
- **Dose reductions** and **temporary dose interruptions** for **safety** reasons are ***permitted at any time*** during the study.

Refer to Section 6.1.1 for additional details.

4.1.2 Study Period 2

This period (Week 13 to Week 24) 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. Decreases or temporary interruptions in the dose of LCI699 for safety reasons are permitted during this period without affecting eligibility for randomization.

Dose adjustments may be managed via a phone call between visits or via an unscheduled visit at the site. Please refer to Section 6.1.1 for details.

In order for a patient to be assessed as a complete responder at Week 24, the following two conditions must be met:

- mUFC ≤ ULN based on urine samples collected at Week 24
- 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; 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.

4.1.3 Study Period 3

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

4.1.3.1 Double-blinding

The Novartis study team (except Global Clinical Supply (GCS))the patient, the investigator, and all other site staff remain blinded to treatment assignment from the time of randomization to the time of database lock for the core period of the study.

4.1.3.2 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 ≤ ULN) from urine samples collected at Week 24. Decreases or temporary interruptions in the dose of LCI699 for safety reasons are permitted and does not affect eligibility for randomization. Randomization is implemented at the Week 26 visit.

Patients that are not eligible for randomization include: partial responders (mUFC reduced by ≥ 50% from baseline, but above ULN) at Week 24, non-responders (mUFC reduced by < 50% from baseline and > ULN) at Week 24, and any patient whose dose was increased above the level established at the end of Week 12 (dose titration) between Week 13 and Week 24. These patients 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.

4.1.3.3 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 (≤ 5mg b.i.d. vs. > 5mg-b.i.d.); and history of pituitary irradiation (yes/no).

4.1.3.4 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.

4.1.3.5 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.

Dose adjustments may be managed via a phone call between visits or via an unscheduled visit at the site. Please refer to Section 6.1.1 for details.

4.1.3.6 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 for reasons other than those described above 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.

4.1.3.7 Monitoring and dosing guidelines on resuming open-label LCI699

Patients that are discontinued from randomized withdrawal due to lack of efficacy as described in Section 4.1.3.6, will resume open-label LCI699 at the time of discontinuation, which will typically occur before Week 34. Patients that are not discontinued during randomized withdrawal will resume open-label LCI699 at the end of randomized withdrawal (Week 34) and thereafter (Study Period 4).

Precaution

The investigator is advised to monitor patients closely upon resuming open-label LCI699, which may occur either during the randomized withdrawal period (if the patient is discontinued from randomized withdrawal), or at Week 34 (if the patent was not discontinued from randomized withdrawal). Week 34 is the time of entry into Study Period 4. Some patients may experience a period of instability with respect to UFC levels and symptoms. In particular, patients with uncontrolled UFC may experience glucocorticoid withdrawal syndrome if UFC is reduced (corrected) too rapidly. Unscheduled visits are permitted as often as needed until UFC stabilizes. In addition, local laboratory results may be used to guide treatment decisions, but all UFC tests must be sent to the central laboratory for later confirmation. This is the only time during the study in which local laboratory results can be used for LCI699 dose decisions.

Upon resuming open-label LCI699, the investigator has the discretion to select the dose, and is advised to consider the following guidelines:

- Patients with a normal UFC during randomized withdrawal should resume the same dose of study drug on re-starting open-label LCI699.
- Patients with uncontrolled UFC that were discontinued from randomized withdrawal are at increased risk of developing glucocorticoid withdrawal syndrome.
  - LCI699 could be prescribed at the same dose that was used at Week 26
  - Alternatively, LCI699 could be prescribed at a lower dose than the one used at Week 26, to reduce the risk of glucocorticoid withdrawal syndrome. With this strategy, it is expected that the dose will need to be titrated upward.
  - It is not recommended to prescribe a dose higher than was used at Week 26, because there may be an excess risk of glucocorticoid withdrawal syndrome, hypocortisolism or adrenal insufficiency.
- Patients whose dose was reduced for safety reasons during the randomized withdrawal period should resume the reduced dose of study drug on re-starting LCI699.
- Patients with temporary interruption of study drug for safety reasons during randomized withdrawal that has resolved by Week 34 are advised to continue the same dose they were receiving at week 34.
- Patients with dose interruption for safety that remains ongoing at week 34 may resume open-label LCI699 at the investigator's discretion, if the patient is expected to remain on study.

At the time of discontinuation from randomized withdrawal due to uncontrolled UFC, or at the end of the randomized withdrawal period (Week 34), whichever occurs first, patients that were randomized to placebo will automatically be crossed-over to open-label LCI699, while patients randomized to LCI699 will remain on LCI699, but in an open-label fashion.

4.1.3.8 Complete response and primary endpoint assessment

In order for a patient to be assessed as a complete responder at Week 34, all of the following conditions must be met:

- mUFC ≤ ULN at Week 34
- Patient was not discontinued during the randomized withdrawal period

The primary endpoint is assessed on the basis of mUFC results at the end of the randomized withdrawal period (Week 34) for all randomized patients. The endpoint compares the complete response rate (proportion of patients with mUFC ≤ ULN) at the end of 8 weeks of randomized withdrawal (at Week 34) between patients randomized to continued LCI699 therapy vs. placebo. Patients who are discontinued during the randomized withdrawal period are not considered complete responders.

4.1.4 Study Period 4

Study Period 4 is a single-arm, open-label therapy (Week 35 to Week 48). At the end of Week 34, all patients receive open-label LCI699 treatment. The investigator has the discretion to select the dose during this period and is advised to consider the guidelines mentioned in Section

4.1.3.7. Once the patient is on open-label LCI699, the dose may remain unchanged, increased, decreased or withheld, depending on the mUFC level, and whether or not there is an AE requiring temporary interruption of study drug. Particularly during the first few weeks of open-label LCI699 treatment (after randomized withdrawal), patients may have unscheduled visits if they report symptoms of continuing hypercortisolism, glucocorticoid withdrawal, hypocortisolism, or any adverse event.

Dose adjustments may be managed via a phone call or via an unscheduled visit at the site. Please refer to Section 6.1.1 for details.

Patients continue open-label therapy until Week 48. 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).

4.1.5 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 16 months 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 16 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 period 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 within 2 months from the initiation visit of the study. If this option is not available, the patient can be offered a local alternative treatment option and should transition within 2 months of the option being available at site; if no local alternative treatment option is available, the patient can stay in the study until the study end (i.e. 16 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.

Dose adjustments if needed after Week 72 during extension period will have to be managed via a scheduled or an unscheduled visit at the site.

4.1.6 Escape

Escape is defined as loss of control of UFC after prior UFC normalization in patients who have completed the dose titration period (Period 1). The following criteria have to be met:

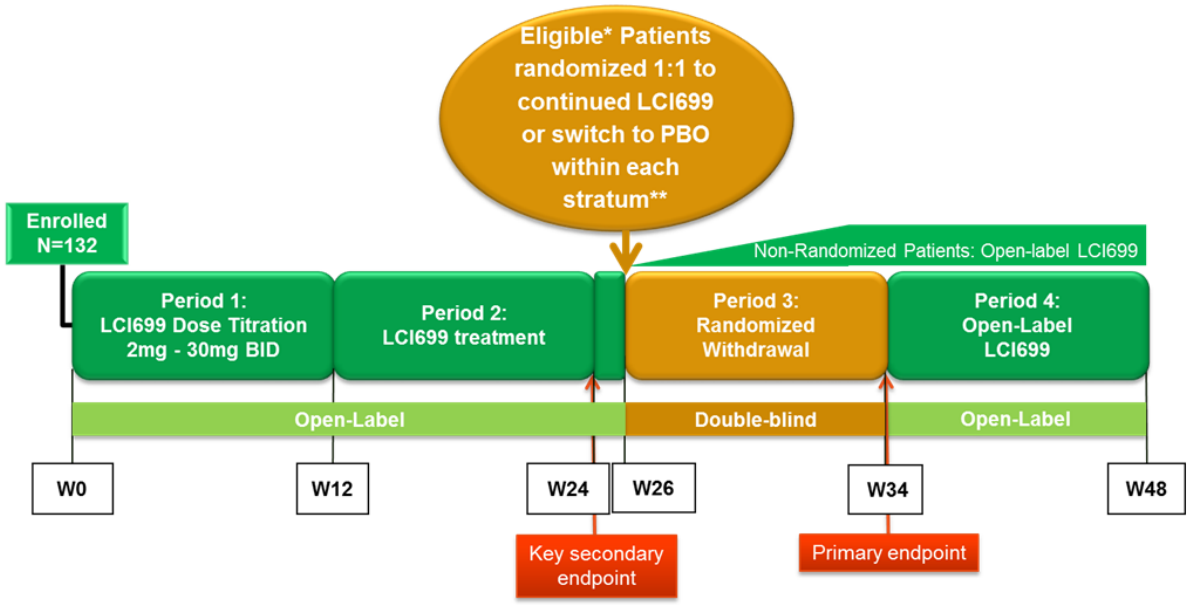
- prior normalization of mUFC has occurred (mUFC≤ULN)
- both the mean UFC and at least 2 individual values contributing to that mUFC have to be >1.5 x ULN
- the escape is not related to a dose interruption or dose reduction due to safety reasons

Patients that are randomized to placebo will not be assessed for escape.

4.1.7 Schematic diagram of core study design

A schematic diagram of the core study design is shown below in Figure 4-3; the optional extension part of the study starting at Week 48 is not represented:

Figure 4-3 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).

4.2 Timing of interim analyses and design adaptations

The study will have no interim efficacy analysis. The Steering Committee (SC) will conduct interim safety analyses as detailed in Section 8.7, the SC Charter and SC Report and Analysis Plan.

4.3 Definition of end of the study

Completion of the study as a whole (last patient last visit) will occur after all patients have completed all assessments as per Table 7-1 to Table 7-3 (core phase), Table 7-4 and Table 7-5 (extension phase) or have discontinued early. 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 16 months after all patients have completed Week 72 or have discontinued early (prior to Week 72). Refer to Section 6.1.5 for details.

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient will be contacted by the investigator or his/her designee. The patient should be seen as soon as possible and the same assessments should be performed as described in Section 7 for

a discontinued or prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5 Population

5.1 Patient population

The study population will be comprised of approximately 132 adult male and female patients with Cushing's disease who have persistent or recurrent hypercortisolism after primary pituitary surgery and/or irradiation, and patients with *de novo* Cushing's disease who are not surgical candidates for medical reasons, or refuse to undergo surgery.

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

Eligibility criteria for entering the randomized withdrawal period are described in Section 4.1.

5.2 Inclusion criteria

Patients must fulfill all of the following criteria to be eligible for inclusion in this study:

1. Written informed consent must be obtained before any assessment is performed.
2. Male or female patients aged 18 - 75 years
3. Patients must have confirmed Cushing's disease that is persistent or recurrent as evidenced by:
   a. mUFC > 1.5 x ULN at screening (the mean of three 24-hour urine samples collected during screening, after completion of the washout period (if applicable), confirmed by the central laboratory and available at Day 1)
   b. Morning plasma ACTH above lower limit of normal
   c. Confirmation of pituitary source of excess ACTH is defined by any of the following three criteria:
      1. MRI confirmation of pituitary adenoma > 6 mm; OR
      2. bilateral inferior petrosal sinus sampling (BIPSS) with either CRH or DDAVP stimulation for patients with a tumor ≤ 6mm. The criteria for a confirmatory BIPSS test are any of the following:
      - Pre-dose central to peripheral ACTH gradient > 2;
      - Post-dose central to peripheral ACTH gradient > 3 after either CRH or DDAVP stimulation
      3. histopathologic confirmation of an ACTH-staining adenoma in patients who have had prior pituitary surgery.
4. Patients with a history of prior pituitary surgery must be at least 30 days post-surgery to be eligible for inclusion in this study.

5. Patients that received glucocorticoid replacement therapy post-operatively must have discontinued such therapy for at least one week, or (5 half-lives), whichever is longer, prior to screening.
6. Patients with de novo Cushing's disease can be included only if they are not considered candidates for surgery (e.g., poor surgical candidates, surgically unapproachable tumors, patients who refuse to have surgical treatment, or surgical treatment is not available)
7. Patients with a history of pituitary irradiation can be included, provided that at least 2 years (stereotactic radiosurgery) or 3 years (conventional radiation) have elapsed from the time of last radiation treatment to the time of enrollment into this study.
8. Patients are permitted to washout current drug therapy to meet these entry criteria if they have a known diagnosis of Cushing's disease. Rescreening can be used as needed to ensure washout is complete. The following washout periods must be completed before baseline efficacy assessments are performed:
    a. Steroidogenesis inhibitors (ketoconazole, metyrapone): 1 week
    b. Pasireotide s.c. (immediate release formulation): 1 week
    c. Dopamine agonists (e.g., cabergoline), or PPAR-gamma agonists (e.g., rosiglitazone, pioglitazone): 4 weeks
    d. Mifepristone : 4 weeks
    e. Pasireotide LAR: 8 weeks
    f. Mitotane: 6 months

5.3 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study:

1. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives at the time of enrollment, whichever is longer; or longer if required by local regulations, and for any other limitation of participation in an investigational trial based on local regulations.
2. History of hypersensitivity to LCI699 or to drugs of similar chemical classes.
3. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
4. Patients with risk factors for QTc prolongation or Torsade de Pointes, including:
    - patients with a baseline QTcF > 450ms for males and QTcF > 460ms for females,
    - personal or family history of long QT syndrome, or concomitant medications known to prolong the QT interval,
    - hypokalemia, hypocalcaemia, or hypomagnesemia, if not corrected before pre-dose Day 1.
5. Pregnant or nursing (lactating) women.
6. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 1 week after completion of dosing. Highly effective contraception methods include:

a. Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
b. Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of bilateral oophorectomy, documentation is required (e.g. operative report, pelvic ultrasound or other reliable imaging method).
c. Male sterilization (at least 6 months prior to screening). For female subjects on the study the vasectomized male partner should be the sole partner for that subject.
d. Combination of any two of the following (a+b or a+c, or b+c):
    a. Use of oral*, injected, or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
    b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
    c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

    *In the case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In case of bilateral oophorectomy, documentation is required (e.g. operative report, pelvic ultrasound or other reliable imaging method).

7. Patients with compression of the optic chiasm due to a macroadenoma or patients at high risk of compression of the optic chiasm (tumor within 2 mm of optic chiasm).
8. Patients who have a known inherited syndrome as the cause for hormone over secretion (i.e. Carney Complex, McCune-Albright syndrome, MEN-1, AIP).
9. Patients with Cushing's syndrome due to ectopic ACTH secretion or ACTH-independent (adrenal) Cushing's syndrome.
10. Patients who have undergone major surgery within 1 month prior to screening.
11. Hypertensive patients with uncontrolled blood pressure defined as SBP > 180 and/or DBP > 100.
12. Diabetic patients with poorly controlled diabetes as evidenced by HbA1c > 9 %.
13. Patients who are not euthyroid as judged by the investigator.
14. Patients who have a history of: congestive heart failure (NYHA Class III or IV), unstable angina, sustained ventricular tachycardia, clinically significant bradycardia, advanced heart block, acute MI less than one year prior to study entry, or clinically significant impairment in cardiovascular function.
15. Patients with moderate to severe renal impairment (estimated GFR < 60 mL/min by the MDRD formula, or serum creatinine > 2.0 x ULN.

16. Patients with liver disease such as cirrhosis, chronic active hepatitis, or chronic persistent hepatitis, or patients with serum ALT/AST > 3 x ULN, or serum total bilirubin > 1.5 x ULN.
17. Patients who have any current or prior medical condition that can interfere with the conduct of the study or the evaluation of its results in the opinion of the investigator or the sponsor's medical monitor.
18. Patients who have a history of alcohol or drug abuse in the 6 month period prior to study treatment.
19. Patients with a history of non-compliance to medical regimens or who are considered potentially unreliable or will be unable to complete the entire study.

6 Treatment

6.1 Study treatment

The study treatment consists of LCI699 and matching placebo, in the form of film-coated tablets for oral administration, in the following tablet strengths: 1 mg, 5 mg, 10 mg, and (depending on availability) 20 mg. Each strength has a unique size, color and imprint (Y1, Y2, Y3 and Y4) on each tablet which can be used for specific identification. (Figure 6-1).

Figure 6-1 Appearance of LCI699 tablets by strength

Each strength of LCI699 (and matching placebo) has a unique size, color and imprint to aid in recognition. The appearance of the actual tablets may vary slightly from the photograph.

- 1 mg: tablets are approximately 6 mm in diameter, with a pale yellow color and Y1 imprint
- 5 mg tablets are approximately 7 mm diameter, with a yellow color and Y2 imprint
- 10 mg tablets are approximately 9 mm in diameter, with a pale orange brown color and Y3 imprint and
- 20 mg tablets are approximately 11 mm in diameter, with a light brown color and Y4 imprint

6.1.1 Dosing regimen

The dosing regimen of LCI699 in the planned pivotal study will be up-titrated according to the following escalation sequence: LCI699 2 mg b.i.d., 5 mg b.i.d., 10 mg b.i.d., 20 mg b.i.d., and 30 mg b.i.d. The up-titration continues till the mUFC ≤ ULN. The maximum dose of LCI699 in this study is 30 mg b.i.d.

Study treatment should be taken twice daily (b.i.d.). For example, a patient on the starting dose of 2 mg b.i.d. dose will take two tablets of 1 mg strength in the morning and two tablets of 1 mg strength in the evening, providing a total daily dose of 4 mg. Study drug should be taken at approximately the same time each day, with about 12 hours between each dose administration. LCI699 can be dosed without regard to food. If vomiting occurs during the course of treatment, patients should not take the study drug again before the next scheduled dose. Patients should be instructed not to make up missed doses.

On study visit days, patients should be reminded to not take the study treatment prior to the site visit to ensure compliance with the pre-dose PK sampling procedure. The morning dose on the visit days should be taken at the site after the pre-dose PK sampling.

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 LCI699 dose is increased if the mean of three urine samples (mUFC) is above normal (> ULN).
- The LCI699 dose is maintained if the mUFC value is in the normal range and the patient does not have signs or symptoms of hypocortisolism or adrenal insufficiency.
- The LCI699 dose is reduced if the mUFC value is < LLN or the patient has signs and symptoms of hypocortisolism or adrenal insufficiency and the mUFC value is in the lower part of the normal range.

Hypocortisolism or adrenal insufficiency is suspected on the basis of clinical signs/symptoms, which may include gastrointestinal symptoms (nausea, vomiting), fatigue, weakness, failure to thrive, morning headache, symptoms consistent with hypoglycemia, or dizziness.

Dose reductions and temporary dose interruptions for safety reasons are permitted at any time during the study. For patients that enter the randomized withdrawal period, both the investigator and the patient are blinded to the randomized treatment assignment from the time of randomization until the time of database lock for the core period of the study.

If hypocortisolism occurs at 2 mg b.i.d., the dose can be lowered to 1 mg b.i.d. or lower, e.g., 1 mg q.d. (once a day) or 1mg q.o.d. (every other day), if needed. Any lower dose other than 1 mg bid is not a standard dose and as mentioned below must be discussed with the sponsor on a case-by-case basis before implementation.

Once the patient's mUFC is controlled (mUFC ≤ ULN) during the dose titration period, intermediate doses (doses other than the standard doses specified in the escalation sequence – LCI699 2 mg b.i.d., 5 mg b.i.d., 10 mg b.i.d., 20 mg b.i.d., and 30 mg b.i.d) can be given. In such cases the same dose should be used in the a.m. and the p.m., as a b.i.d. regimen, if possible, to ensure consistent drug exposure.

Permitted intermediate dose levels are: 3, 7 and 15 mg b.i.d.

Any doses other than one of the standard planned doses for the dose escalation sequence or the permitted intermediate doses must be discussed with the sponsor on a case-by-case basis before implementation.

The investigators and other site staff should be aware that the use of non-standard doses increases the complexity of dispensing drug to the patient, and self-administration of drug by the patient. Increased complexity of self-administration by the patient may increase the risk of dosing errors.

Communication and implementation of dose changes:

If a dose change is needed, this will typically occur between scheduled visits. The dose change should be done as soon as possible after receipt of mUFC results (e.g. ideally within 24 hours). Sites should inform patients of the dose change via phone contact or an unscheduled visit prior to the next scheduled visit, as noted in Section 4.1.1.

If the dose adjustment is communicated by telephone:

- the site must confirm the current dose the patient is taking
- Instruct the patient on how to administer the new dose, and ensure that the patient has adequate supplies at the new dose to last until the next scheduled visit. The dose instructions must include the tablet strength(s), number of tablets, and time of day administered (morning or evening); this should be done individually for morning and evening doses. The patient should repeat back all dosing instructions.
- The patient should also be questioned on the signs and symptoms of glucocorticoid withdrawal/hypocortisolism/adrenal insufficiency and other abnormal signs and symptoms with any positive symptom(s) graded for severity and reported as an AE and this should be taken into account when making the dose adjustment.
- All phone communications should be included in the source documents at the site. Also, refer to Section 6.3.1 for details on dose modification and dose delay.

If, in the investigator's judgment, the patient is not reliable or cannot safely make the dose adjustment at home, the patient could return to the site for an unscheduled visit prior to the next scheduled visit to receive instructions regarding the dose change under the direct supervision of the site staff.

If the dose is maintained without change, the patient does not need to return to the site until the next scheduled study visit. However, it is still recommended that the site contact the patient to: confirm the current dose; ask about potential signs and symptoms of hypocortisolism or adrenal insufficiency; remind the patient to continue to take the same dose of LCI699.

At the time of the next study visit, the patient must:

- Return all unused tablets to the site for drug accountability
- Receive medication supplies for the new dose as specified by the IRT system if there is no dose change needed for safety, together with the next higher and lower standard dose(s). The IRT system specifies which study drug bottles (kits) are to be dispensed to the patient. **It is very important** for the site personnel and the patient to be aware that it is possible that more than one tablet strength may be dispensed at the same visit.

- Receive detailed written instructions on how to administer the new dose and dosing schedule. Dose instructions should include the tablet strength, number of tablets to take and the time of the day (morning or evening); the instructions should be given individually for the morning and evening dose, rather than "twice per day." Patients should be asked to read back all documented instructions to ensure comprehension. Such explicit written instructions are particularly important in view of the possibility of cognitive impairment and/or mood disorder in the study population. A patient dosing instruction card is recommended as a tool to provide the written instructions to allow the patient a means of confirming the strength of any study drug tablet by visual inspection, if needed, by comparison to photographs of each tablet strength which are on the card.

It is expected that patients will be seen urgently in an unscheduled visit at the site in the event of signs/symptoms of suspected hypocortisolism or adrenal insufficiency or any AE that requires study drug interruption with or without glucocorticoid therapy. However, there may be occasions in which the patient has been seen at another health care facility, or has called in to report symptoms; in these cases, patients should be advised to come to the site as soon as possible if it is safe, or go to the nearest hospital emergency room.

For further details on dosing regimen for each study period, please refer to Section 4.1 "Description of study design."

6.1.2 Ancillary treatments

Not applicable.

6.1.3 Rescue medication

Not applicable.

6.1.4 Guidelines for continuation of treatment

LCI699 therapy (or matching placebo) is continued unless it must be interrupted or discontinued for safety or other reasons. See Section 6.3 'Dose modifications' for details.

6.1.5 Treatment duration

The treatment duration is 48 weeks in the core phase of the study, and patients will have the option to continue treatment in the extension phase; patients who wish to enter the extension period must be re-consented at Week 48. The optional extension period will end 16 months after all patients have completed Week 72 or 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 16 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 period 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 within 2 months from the initiation visit of the study. If this option is not available, the patient can be offered a local alternative treatment option and should

transition within 2 months of the option being available at site; if no local alternative treatment option is available, the patient can stay in the study until the study end (i.e. 16 months after the last ongoing 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.

Patients may be discontinued from treatment with the study drug earlier if unacceptable toxicity has been experienced, and/or treatment is discontinued at the discretion of the investigator or the patient.

6.2 Dose escalation guidelines

Not Applicable. This is not a dose escalation study. Please refer to Section 6.1.1 for dose titration procedure.

6.3 Dose modifications

6.3.1 Dose modification and dose delay

Dose reductions and temporary dose interruptions for safety reasons are permitted at any time during the study. Both the investigator and the patient are blinded to the randomized treatment assignment during randomized withdrawal from the time of randomization until the time of database lock for the core period of the study. Dose reductions may be required for AEs suspected to be related to LCI699.

A unique feature of LCI699 treatment in patients with Cushing's disease is that regardless of suspected drug causality, an AE may require not only interruption of study drug, but also stress doses of glucocorticoids until the AE has resolved.

Please refer to Section 4.1 "Description of study design" and Section 6.1.1 "Dosing regimen" for further information about dose and dosing regimen during various periods during the trial.

Patients with suspected acute, symptomatic hypocortisolism or adrenal insufficiency may require emergency unblinding (see Section 8.3) because such an AE is potentially life threatening. Unblinding does not apply during the open-label period throughout the trial (for patients that are not randomized), or the open-label period from the time of the first dose of LCI699 to until the time of randomization (for patients that are randomized).

Hypocortisolism or adrenal insufficiency is suspected on the basis of clinical signs/symptoms, which may include gastrointestinal symptoms (nausea, vomiting), fatigue, weakness, failure to thrive, morning headache, symptoms consistent with hypoglycemia, dizziness. When hypocortisolism or adrenal insufficiency is suspected, the investigator may order urgent local laboratory testing, including serum cortisol to help differentiate glucocorticoid withdrawal symptoms from hypocortisolism or adrenal insufficiency. The turnaround time for central laboratory results in this circumstance is unacceptably long from a clinical safety viewpoint.

For patients whose dose needs to be fine-tuned to provide the requested efficacy or are unable to tolerate the protocol-specified dosing schedule, dose adjustments to other than standard dose levels (2, 5, 10, 20 and 30 mg respectively b.i.d) are permitted in order to keep the patient on

study drug. The following guidelines should be followed. These changes must be recorded on the Dosage Administration Record CRF.

Table 6-1 Dose Modification Guidelines[1] for LCI699-suspected toxicities

Toxicity	Suggested Actions
Symptomatic hypocortisolism or adrenal insufficiency	If the investigator at any time suspects hypocortisolism or adrenal insufficiency, they can immediately interrupt study drug and initiate replacement with glucocorticoids. Emergency un-blinding may be considered if this occurs during the double-blind randomized withdrawal period of the study. Upon recovery as assessed by the investigator*, glucocorticoid therapy can be tapered as tolerated, and study drug can be re-started. The decision to restart study drug will be made by the investigator. The AE and associated treatments with changes to study drug need to be appropriately documented in the eCRF. *Recovery is assessed clinically by the investigator. A general guideline is that glucocorticoid taper can begin when mUFC is in the upper part of the normal range or > ULN, and study drug can be re-started if the patient is clinically stable off glucocorticoid therapy for at least one week, and the mUFC is normal or > ULN.
Persistent asymptomatic hypocortisolism (mUFC < LLN) at the lowest dose of LCI699 (1 mg every other day)	The investigator can interrupt study drug and restart at the same dose as clinically indicated.
Glucocorticoid withdrawal syndrome	Reduce or withhold dose until improved
*Hypotension (mild, reversible)	Reduce or withhold dose until improved
*Hypertension	Reduce or withhold dose until improved; consider ACE inhibitors if appropriate for treatment of hypertension, or spironolactone as a second line treatment, particularly if hypokalemia is present. ACE inhibitors and spironolactone should not be used in combination.
*Weight gain, edema	Reduce or withhold dose until improved; consider spironolactone for treatment of edema.
*Hypokalemia	Consider reducing or withholding dose until improved; replace potassium; consider spironolactone or eplerenone for prevention and treatment of hypokalemia
*Hyperkalemia	Consider reducing or withholding dose until improved; if on spironolactone or eplerenone, reduce or withhold; treat with kayexalate and other potassium lowering therapies as needed.
*Hirsutism (women only)	Reduce or withhold dose until improved; review testosterone level; consider spironolactone, cyproterone acetate or finasteride per local guidelines.
*Acne (women or men)	Reduce or withhold dose until improved; review testosterone level; consider spironolactone, cyproterone acetate or finasteride per local guidelines.
[1]The investigator must specify the reduced dose of study drug (LCI699/Placebo) during the randomized withdrawal period, and the reduced dose of LCI699 during the open-label periods of the study. * Abbreviations: UFC, 24-hour urine free cortisol; ULN, upper limit of the normal reference range; LLN, lower limit of the normal reference range.	

In addition, any AE, regardless of suspected drug causality, may require interruption of LCI699 and replacement or stress doses of glucocorticoid therapy until resolution of the event.

- Upon recovery from the AE, the investigator may consider re-starting LCI699 if the dose interruption has been ≤ 14 days.

- If the dose interruption has been > 14 days, then the patient should be observed. If mUFC rises to above the ULN, and has been off glucocorticoid therapy for at least one week, LCI699 may be re-started.

If the patient has interruption of LCI699 for more than 4 weeks, the investigator should consider early discontinuation from the study. Patients that had interruption of LCI699 and mUFC remains ≤ ULN off LCI699 should remain on study for observation.

These changes must be recorded on the Dosage Administration Record CRF.

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

Table 6-2 Criteria for interruption and re-initiation of LCI699 for abnormal liver function

Isolated total Bilirubin elevation	
> ULN – 1.5 x ULN	Maintain dose level
> 1.5 - 3.0 x ULN	Withhold study drug. Monitor liver function tests (LFT)[a] weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN: If resolved in ≤ 14 days, then maintain dose level If resolved in > 14 days, then decrease by one dose level.
> 3.0 - 10.0 x ULN*	Withhold study drug. Monitor LFTs[a] weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN: If resolved in ≤ 14 days, then decrease by one dose level. If resolved in > 14 days, then discontinue patient from study drug treatment. The patient should be monitored weekly (including LFTs[a]), or more frequently if clinically indicated, until total bilirubin has returned to baseline or stabilized over 4 weeks.
> 10.0 x ULN*	Discontinue patient from study drug treatment The patient should be monitored weekly (including LFTs[a]), or more frequently if clinically indicated, until total bilirubin has returned to baseline or stabilized over 4 weeks.
Isolated AST or ALT elevation	
> ULN - 3.0 x ULN	Maintain dose level
> 3.0 - 5.0 x ULN	Maintain dose level. Repeat LFTs[a] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs[a] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN
> 5.0 - 10.0 x ULN	Withhold study drug. Repeat LFTs[a] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[a] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN. Then: If resolved in ≤ 14 days, restart study drug and maintain dose level If resolved in > 14 days, restart study drug and decrease dose by one level If not resolved after 4 weeks, discontinue patient from study treatment

> 10.0 x ULN	Discontinue study drug. Repeat LFTs[a] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[a] weekly, or more frequently if clinically indicated, until resolved to ≤3 x ULN.
Combined [b, c] elevations of AST or ALT and total bilirubin	
For patients with normal baseline ALT and AST and total bilirubin value: AST or ALT >3.0 x ULN combined with total bilirubin >2.0 x ULN without evidence of cholestasis[c] OR For patients with elevated baseline AST or ALT or total bilirubin value: [AST or ALT>2x baseline AND > 3.0 xULN] OR [AST or ALT > 8.0 xULN], **combined with** [total bilirubin >2x baseline AND >2.0 xULN	Permanently discontinue patient from study drug treatment. Repeat as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs[a]), or more frequently if clinically indicated, until AST, ALT, or bilirubin have returned to baseline or stabilized over 4 weeks. Refer to Section 6.3.3 for additional follow-up evaluations as applicable.
All dose modifications should be based on the worst preceding toxicity. a. Core LFTs consist of ALT, AST, GGT, total bilirubin (fractionated [direct and indirect], if total bilirubin > 2.0 x ULN), and alkaline phosphatase (fractionated [quantification of isoforms], if alkaline phosphatase > 2.0 x ULN.) b. "Combined" defined as: total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold. If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of total bilirubin and isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g. discontinue treatment at the situation when omit dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start the treatment either at the same dose or at one dose lower if meeting a criterion for dose reduction c. "Cholestasis" defined as: ALP elevation (>2xULN and R value (ALT/ALP in x ULN) < 2). Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury *Note: If total bilirubin > 3.0 x ULN is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level and continue treatment at the discretion of the investigator.	

6.3.2 Follow-up for toxicities

Please refer to Section 6.3.1 and Section 8.1.3.

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

Patients with transaminase increase combined with Total Bilirubin (TBIL) increase may be indicative of potential DILI, and should be considered as clinically important events.

The threshold for potential DILI may depend on the patient's baseline AST/ALT and TBIL value; patients meeting any of the following criteria will require further follow-up as outlined below:

- For patients with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN
- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as ALP elevation > 2.0 x ULN with R value < 2.

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

In the absence of cholestasis, these patients should be immediately discontinued from study drug treatment, and repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment and evaluation for the possibility of liver lesions, obstructions/compressions, etc.

- Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/ international normalized ratio (INR) and alkaline phosphatase.
- A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.
- Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.
- Obtain PK sample, as close as possible to last dose of study drug
- Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as "medically significant", thus, met the definition of SAE (Section 8.2.1) and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

6.3.4 Anticipated risks and safety concerns of the study drug

Anticipated drug-related risks are summarized in Section 2.7. Many of the safety concerns and recommendations for actions are reviewed in Section 6.3.1 "Dose modification and dose delay."

Additional anticipated risks are summarized in Section 8.1.3 "Adverse events of special interest." Two of these AEs are described in greater detail: the potential for QT prolongation (Section 8.1.3.1), and glucocorticoid withdrawal, hypocortisolism or adrenal insufficiency (Section 8.1.3.2). Recommendations for QT prolongation monitoring and management are provided in Section 7.2.2.7. Other AEs of special interest for LCI699 (either reported or anticipated based on the mechanism of action of the drug) include: cardiac arrhythmia, corticotroph tumor progression (Nelson's syndrome) and potential associated symptoms (visual field loss, cranial nerve palsy, diplopia, and hyperpigmentation); these particular AEs may require premature discontinuation from the study.

For a comprehensive review of safety, see the [Investigator's Brochure].

6.4 Concomitant medications

Stable doses of concomitant medications (except those for hypercortisolism) are allowed during the study. All pre-existing concomitant medications should be recorded at study start. The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of the study. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient signs the informed consent must be listed on the Concomitant medications/Significant non-drug therapies after start of study CRF.

All prescription medications and over-the-counter drugs taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant Medications/ Non-Drug Therapies page of the CRF. Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation dates and the reason for therapy.

All concomitant medications received during the study should be reported on the CRF, and include the drug name (specific trade name), the single dose and unit, the frequency and route of administration, start and discontinuation dates and the reason for therapy. Medications used for the treatment of hypertension, diabetes or impaired glucose tolerance, and hyperlipidemia, in particular, require this detailed information as part of the efficacy assessment.

6.4.1 Permitted concomitant therapy

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Concomitant Medications CRF. Spironolactone and eplerenone are permitted for the treatment or prevention of study drug-related edema or hypokalemia. The use of these drugs should be done with close monitoring for the potential risk of severe hyperkalemia, which is further increased if renal insufficiency is present.

Spironolactone, cyproterone acetate or finasteride for treatment of hirsutism are approved in some countries and are not prohibited.

Medications that are metabolized by CYP450 enzymes

In vitro drug metabolism studies show that LCI699 is a potential inhibitor of CYP1A2, CYP2C19, CYP2D6, CYP3A4/5 and CYP2E1, and may consequently increase exposure to drugs metabolized by this enzyme.

In a clinical DDI study, LCI699 was found to be a moderate inhibitor of CYP1A2 (2.5-fold increase in substrate exposure), a weak to moderate inhibitor of CYP2C19 (1.9-fold increase in substrate exposure), and a weak inhibitor of CYP2D6 and CYP3A4/5 (1.5-fold increase in substrate exposure). Therefore concomitant medications that are known substrates of these enzymes (see Appendix 2) should be used with caution.

The patient and the Investigator should be aware of potential signs of overdose of the concomitant medication and in the event of suspected toxicities; administration of either the substrate or LCI699 should be discontinued according to Investigators' judgment

6.4.2 Prohibited concomitant therapy

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

- Other drug treatments for Cushing's disease;
- Medications with a "known risk to cause Torsades des Pointes (TdP)" and "possible risk to cause TdP";
- Eplerenone and glucocorticoids, except under certain conditions:
  - Eplerenone may be used if necessary in acute post-myocardial infarction management, and in the event of refractory hypokalemia in patients with hypertension or edema; glucocorticoids may be used as required for the short-term treatment of hypocortisolism or adrenal insufficiency.
  - Glucocorticoids (e.g., prednisone, prednisolone, and dexamethasone) may be used as required for the short-term treatment of hypocortisolism or adrenal insufficiency. If glucocorticoids are used in stress doses, or as replacement therapy, for > 4 weeks, then the investigator should consider temporary interruption of LCI699, weaning and discontinuation of glucocorticoid therapy, or early discontinuation from the study.

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

Preclinical and clinical data indicate that there is a risk of QTc prolongation in humans (see Section 8.1.3.1). Therefore, the use of medications with a "known risk to cause TdP" and with a "possible risk to cause TdP" concomitantly with LCI699 is prohibited.

If a patient requires a long-term medication from the two categories mentioned above, and there is no appropriate alternative medication available, they should be discontinued from the study.

However, if a patient requires such a drug for short-term therapy, e.g., antibiotics for active infection, then the LCI699 treatment may be interrupted temporarily while this drug is administered after a thorough risk-benefit assessment. This does not require the patient to discontinue from the study prematurely. Washout periods for LCI699 and the short-term prohibited drug in many cases may not be possible; this is acceptable if the benefit of the drug outweighs the risk of withholding LCI699 therapy in the investigator's judgment. In such cases, a discussion with the Novartis Medical Monitor is recommended.

Please refer to Appendix 3 for an e-link to a list of medications that have a "known risk to cause TdP" and "possible risk to cause TdP". Investigators are advised to utilize this website when considering the addition of a new concomitant medication, as the lists are periodically updated. If necessary, a discussion can be held with the Novartis Medical Monitor when considering the use of medications with a "known risk to cause TdP" and with a "possible risk to cause TdP"

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient numbering

Each patient is identified in the study by a Patient Number (Patient No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Patient No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each patient is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Patient No. available to the investigator.

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

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

6.5.2 Treatment assignment or randomization

At week 26, and based upon the mUFC results from the Week 24 assessment, and the LCI699 dose at week 26 compared to week 12, patients will either:

- Not be randomized, and continue LCI699 treatment according to the schedule in Table 7-3.
- Be randomized to one of the two treatment assignments (LCI699 or placebo) in a 1:1 ratio (Section 4.1 and Section 6.1).

Randomization will be stratified by LCI699 dose at Week 24 (≤ 5mg b.i.d. vs. > 5mg b.i.d.); and history of pituitary irradiation (yes/no).

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

Prior to dosing on Week 26, all patients who fulfill mUFC criteria will be randomized via IRT to one of the treatment arms. The investigator or his/her delegate will call or log on to the IRT and confirm that the patient fulfills mUFC criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the patient. The randomization number will not be communicated to the caller.

The randomization scheme for patients will be reviewed and approved by a member of the Biostatistics Quality Assurance Group. Specific instructions for IRT will be provided separately to each study site.

6.5.3 Treatment blinding

Patients, investigators, site personnel, and the Novartis Clinical Trial Team (except GCS, the bioanalyst and the bioanalytical study monitor) will remain blinded to the identity of the randomized treatment assignments from the time of randomization (Week 26) until database lock, using the following methods: (1) randomization data are kept strictly confidential until the time of treatment unblinding. (2) the identity of the randomized treatment assignments will be concealed by the use of matching placebo during the randomized withdrawal period. The matching placebo is identical in packaging, labeling, schedule of administration, and appearance (color, size, and weight). Novartis Global Clinical Supply department members will be unblinded in order to prepare the study drug supplies.

Unblinding before database lock will only occur in the case of emergencies (Section 8.3 "Emergency unblinding").

6.6 Study drug preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug(s) will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

Patients may be dispensed bottles of more than one tablet strength at the same visit. For example, at Visit 2, when the patient is on 2 mg b.i.d dose level, the patient would be provided with bottles of 1 mg and 5 mg tablet strengths to cover for the current dose level, any dose decrease in case of safety concerns and any up-titration to 5 mg b.i.d. Consequently, to ensure patient safety, it is **very important** that site staff educate the patient on how to recognize the tablet strength dispensed at each visit, both on the bottle labels, and by the appearance of tablets by tablet strength.

Also, refer to Section 6.1.1 for details on dosing regimen, communication and implementation of dose changes

Table 6-3 Preparation and dispensing

Study treatments	Dispensing	Preparation
LCI699 or placebo (1 mg, 5 mg, 10 mg and (depending on availability) 20 mg)	Tablets including instructions for administration are dispensed by study personnel on an outpatient basis. Patients will be provided with adequate supply of study treatment for self-administration at home until at least their next scheduled study visit (including any dose increase required in between visits). **More than one tablet strength may be dispensed to patients at the same visit.**	Not applicable

6.6.1 Study drug packaging and labeling

LCI699/placebo will be supplied as 1 mg, 5 mg, 10 mg and (depending on availability) 20 mg film coated tablets, and will be given orally twice a day.

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

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

Table 6-4 Packaging and labeling

Study treatments	Packaging	Labeling (and dosing frequency)
LCI699 or placebo (1 mg, 5 mg, 10 mg and (depending on availability) 20 mg)	Tablets in bottles	LCI699, LCI699/Placebo (b.i.d.)

6.6.2 Drug supply and storage

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

Table 6-5 Supply and storage of study treatment

Study treatments	Supply	Storage
LCI699 or placebo	Centrally supplied by Novartis	Refer to study treatment label

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit using tablets counts and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

6.6.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug

accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.6.3.3 Handling of other study treatment

Not applicable.

6.6.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate. Study drug destruction at the investigational site will only be permitted if authorized by Novartis in a prior agreement and if permitted by local regulations.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1, Table 7-2, Table 7-3, Table 7-4, Table 7-5 list all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation. The table indicates which assessments produce data to be entered into the database (D) or remain in source documents only (S) ("Category" column).

Table 7-6, Table 7-7, Table 7-8, Table 7-9, Table 7-10, Table 7-11, Table 7-12, Table 7-14 and Table 7-15 list all of the assessments required for the collection plan for Imaging and Disease Assessment, Clinical Laboratory parameters, ECG, PK samples, [redacted].

Patients who discontinue study treatment before visit 777 (if patient is in the core phase of the study) or 778 (if patient is in any year of the extension phase of the study), should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the EOT visit will be performed.

Table 7-1 Visit evaluation schedule – Dose escalation and treatment periods

	Category	Protocol Section	Screening	Baseline	Dose escalation period							EOT titration	Treatment period		
Visit Number			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**775**	**10**	**11**	**12**
Day			**-35 to -8**	**-7 to -1**	**1**	**15**	**29**	**43**	**57**	**71**	**85**		**113**	**141**	**169**
week			**-5 to -2**	**-1**	**0**	**2**	**4**	**6**	**8**	**10**	**12**		**16**	**20**	**24**
Obtain Informed consent	D	7.1.1.	x												
IWRS/IRT	S		x	x	x	x	x	x	x	x	x		x	x	x
Patient history															
Demography	D	7.1.1.3.	x												
Inclusion/Exclusion criteria	D	5.2, 5.3 & 7.1.1	x	x											
Relevant medical history/Current medical conditions	D	7.1.1.3.	x												
Cushing's Disease history/prior therapy	D	7.1.1.3.	x												
Prior/concomitant medication	D	7.1.1.3.	As required												
Physical examination	S	7.2.2.1.	x	x		x	x	x	x	x	x		x	x	x
Body height	D	7.2.2.3.	x												
Body weight	D	7.2.2.3.	x	x		x	x	x	x	x	x		x	x	x
Waist circumference	D	7.2.2.3.	x	x		x	x	x	x	x	x		x	x	x
Vital signs															
Body temperature	D	7.2.2.2.	x	x		x	x	x	x	x	x		x	x	x
Blood pressure/Pulse rate	D	7.2.2.2.	x	x		x	x	x	x	x	x		x	x	x
Laboratory assessments															
Hematology	D	7.2.2.4.1.	x	x			x		x		x		x	x	x
Chemistry - full	D	7.2.2.4.2.	x	x			x		x		x		x	x	x
Chemistry - partial	D	7.2.2.4.2.				x		x		x					
Thyroid Panel	D	7.2.2.4.5.		x							x				x

	Category	Protocol Section	Screening	Baseline	Dose escalation period							EOT titration	Treatment period		
Visit Number			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**775**	**10**	**11**	**12**
Day			**-35 to -8**	**-7 to -1**	**1**	**15**	**29**	**43**	**57**	**71**	**85**		**113**	**141**	**169**
week			**-5 to -2**	**-1**	**0**	**2**	**4**	**6**	**8**	**10**	**12**		**16**	**20**	**24**
Luteinizing Hormone (LH) and Follicle stimulating hormone (FSH)	D	7.2.2.4.6.		x		x					x				x
Coagulation	D	7.2.2.4.4.		x							x				
Urinalysis	D	7.2.2.4.3.	x	x		x	x	x	x	x	x		x	x	x
Pregnancy test (serum)	D	7.2.2.4.8.	x	x											
Pregnancy test (urine)	D	7.2.2.4.8.				x	x	x	x	x	x		x	x	x
Efficacy Assessment															
24-hour Urinary Free Cortisol and creatinine	D	7.2.1.1.	x	x		x	x	x	x	x	x		x	x	x
Serum testosterone and estradiol	D	7.2.2.4.6.		x		x					x				x
Serum Androstenedione, DHEAS, Estrone	D	7.2.2.4.6.		x		x					x				x
Plasma ACTH, serum cortisol	D	7.2.2.4.6.		x		x	x	x	x	x	x		x	x	x
Serum 11-deoxycortisol	D	7.2.2.4.6.		x		x					x				x
Serum aldosterone	D	7.2.2.4.6.		x		x					x				x
Renin	D	7.2.2.4.6.		x		x					x				x
[redacted]															
Serum11-Deoxycorticosterone	D	7.2.2.4.6.		x		x					x				x
Fasting serum Insulin and plasma glucose	D	7.2.2.4.7.		x							x				x
HbA1C	D	7.2.2.4.7.	x	x							x				x
Safety															
Adverse Events	D	8.1.	As required												
12 Lead safety ECG assessment	D	7.2.2.6.2.	x	x	x	x	x	x	x	x	x		x	x	x
12-Lead 24-hour Holter ECG recording	D	7.2.2.6.1.		x		x					x				x

	Category	Protocol Section	Screening	Baseline	Dose escalation period							EOT titration	Treatment period		
Visit Number			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**775**	**10**	**11**	**12**
Day			**-35 to -8**	**-7 to -1**	**1**	**15**	**29**	**43**	**57**	**71**	**85**		**113**	**141**	**169**
week			**-5 to -2**	**-1**	**0**	**2**	**4**	**6**	**8**	**10**	**12**		**16**	**20**	**24**
[redacted]															
Pituitary MRI (or CT)	D	7.2.2.5.		x											x
Photography	D	7.2.1.2.		x							x				x
DXA scan	D	7.2.1.3.		x											
Patient Reported Outcomes															
HRQoL EQ-5D-5L, CushingQoL, Beck Depression Inventory	D	7.2.6.		x			x		x		x				x
Study Drug administration	D	6.1.1.			continuous b.i.d. dosing										
PK sampling	D	7.2.3.			x	x	x	x	x	x	x		x	x	x
Serum cortisol, salivary cortisol, plasma ACTH (China subset)	D	7.2.2.4.6.		x	x	x	x	x	x	x	x		x	x	x
Serum cortisol (**Extensive PK subset**)	D	7.2.2.4.6.			x	x	x	x	x	x	x		x	x	x
[redacted]															
End of treatment titration form	D											x			

Table 7-2 Visit evaluation schedule – Randomized withdrawal and open label period for randomized patients

	Category	Protocol Section	Randomized Withdrawal period					EOT randomized withdrawal period	Open Label period			EOT core	Study completion
Visit Number			**13**	**14**	**15**	**16**	**17**	**776**	**18**	**19**	**20**	**777**	**779**
Day			**183**	**197**	**211**	**225**	**239**		**253**	**281**	**309**	**337**	**30 days from last dose**
week			**26**	**28**	**30**	**32**	**34**		**36**	**40**	**44**	**48**	
IWRS/IRT	S		x	x	x	x	x		x	x	x	x	x
Prior/concomitant medication	D	7.1.1.3.	As required										
IWRS/IRT Randomization	S		x										
Physical examination	S	7.2.2.1.	x	x	x	x	x		x	x	x	x	x
Body weight	D	7.2.2.3.	x	x	x	x	x		x	x	x	x	x
Waist circumference	D	7.2.2.3.	x	x	x	x	x		x	x	x	x	x
Vital signs													
Body temperature	D	7.2.2.2.	x	x	x	x	x		x	x	x	x	x
Blood pressure/Pulse rate	D	7.2.2.2.	x	x	x	x	x		x	x	x	x	x
Laboratory assessments													
Hematology	D	7.2.2.4.1.	x	x	x	x	x		x	x	x	x	x
Chemistry - full	D	7.2.2.4.2.	x		x		x		x	x	x	x	x
Chemistry - partial	D	7.2.2.4.2.		x		x							
Thyroid Panel	D	7.2.2.4.5.					x					x	x
Luteinizing Hormone (LH) and Follicle stimulating hormone (FSH)	D	7.2.2.4.6.					x					x	x
Coagulation	D	7.2.2.4.4.										x	x
Urinalysis	D	7.2.2.4.3.	x	x	x	x	x		x	x	x	x	x
Pregnancy test (urine)	D	7.2.2.4.8.	x	x	x	x	x		x	x	x	x	x
Efficacy Assessment													
24-hour Urinary Free Cortisol and creatinine	D	7.2.1.1.	x	x	x	x	x		x	x	x	x	x
Serum testosterone and estradiol	D	7.2.2.4.6.					x					x	x

	Category	Protocol Section	Randomized Withdrawal period					EOT randomized withdrawal period	Open Label period			EOT core	Study completion
Visit Number			**13**	**14**	**15**	**16**	**17**	**776**	**18**	**19**	**20**	**777**	**779**
Day			**183**	**197**	**211**	**225**	**239**		**253**	**281**	**309**	**337**	**30 days from last dose**
week			**26**	**28**	**30**	**32**	**34**		**36**	**40**	**44**	**48**	
Serum Androstenedione, DHEAS, Estrone	D	7.2.2.4.6.					x					x	x
Plasma ACTH, serum cortisol	D	7.2.2.4.6.	x	x	x	x	x		x	x	x	x	x
Serum 11-deoxycortisol	D	7.2.2.4.6.					x					x	x
Serum aldosterone	D	7.2.2.4.6.					x					x	x
Renin	D	7.2.2.4.6.					x					x	x
[redacted]													
Serum 11-Deoxycorticosterone	D	7.2.2.4.6.					x					x	x
Fasting serum Insulin and plasma glucose	D	7.2.2.4.7.	x	x	x	x	x					x	x
HbA1C	D	7.2.2.4.7.	x	x	x	x	x					x	x
Safety													
Adverse Events	D	8.1.	As required										
12 Lead safety ECG assessment	D	7.2.2.6.2.	x	x	x	x	x		x	x	x		x
12-Lead 24-hour Holter ECG recording	D	7.2.2.6.1.										x	
[redacted]													
Imaging													
Pituitary MRI (or CT)	D	7.2.2.5.										x	
Photography	D	7.2.1.2.					x					x	
DXA scan	D	7.2.1.3.										x	
Patient Reported Outcomes													
HRQoL EQ-5D-5L, CushingQoL, Beck Depression Inventory	D	7.2.6.	x	x	x	x	x					x	
Study Drug administration	D	6.1.1.	continuous b.i.d. dosing										
PK sampling	D	7.2.3.	x	x	x	x	x		x	x	x	x	

	Category	Protocol Section	Randomized Withdrawal period					EOT randomized withdrawal period	Open Label period			EOT core	Study completion
Visit Number			**13**	**14**	**15**	**16**	**17**	**776**	**18**	**19**	**20**	**777**	**779**
Day			**183**	**197**	**211**	**225**	**239**		**253**	**281**	**309**	**337**	**30 days from last dose**
week			**26**	**28**	**30**	**32**	**34**		**36**	**40**	**44**	**48**	
Serum cortisol, salivary cortisol, plasma ACTH (China subset)	D	7.2.2.4.6.	x	x	x	x	x		x	x	x	x	
Serum cortisol (Extensive PK subset)	D	7.2.2.4.6.	x	x	x	x	x		x	x	x	x	
[redacted]													
End of randomized withdrawal period form	D							x					
End of treatment core form	D											x	
End of study form	D												x

Table 7-3 Visit evaluation schedule – Randomized withdrawal and open label period for non randomized patients

	Category	Protocol Section	Randomized Withdrawal period					EOT randomized withdrawal period	Open Label period			EOT core	Study completion
Visit Number			**13**	**14**	**15**	**16**	**17**	**776**	**18**	**19**	**20**	**777**	**779**
Day			**183**	**197**	**211**	**225**	**239**		**253**	**281**	**309**	**337**	**30 days from last dose**
week			**26**	**28**	**30**	**32**	**34**		**36**	**40**	**44**	**48**	
IWRS/IRT	S		x		x		x		x	x	x	x	x
Prior/concomitant medication	D	7.1.1.3.	As required										
IWRS/IRT Randomization	D		x										
Physical examination	S	7.2.2.1.	x		x		x		x	x	x	x	x
Body weight	D	7.2.2.3.	x		x		x		x	x	x	x	x
Waist circumference	D	7.2.2.3.	x		x		x		x	x	x	x	x
Vital signs													
Body temperature	D	7.2.2.2.	x		x		x		x	x	x	x	x
Blood pressure/Pulse rate	D	7.2.2.2.	x		x		x		x	x	x	x	x
Laboratory assessments													
Hematology	D	7.2.2.4.1.	x		x		x		x	x	x	x	x
Chemistry - full	D	7.2.2.4.2.	x		x		x		x	x	x	x	x
Thyroid Panel	D	7.2.2.4.5.					x					x	x
Luteinizing Hormone (LH) and Follicle stimulating hormone (FSH)	D	7.2.2.4.6.					x					x	x
Coagulation	D	7.2.2.4.4.										x	x
Urinalysis	D	7.2.2.4.3.	x		x		x		x	x	x	x	x
Pregnancy test (urine)	D	7.2.2.4.8.	x		x		x		x	x	x	x	x
Efficacy Assessment													
24-hour Urinary Free Cortisol and creatinine	D	7.2.1.1.	x		x		x		x	x	x	x	x
Serum testosterone and estradiol	D	7.2.2.4.6.					x					x	x
Serum Androstenedione, DHEAS, Estrone	D	7.2.2.4.6.					x					x	x

	Category	Protocol Section	Randomized Withdrawal period					EOT randomized withdrawal period	Open Label period			EOT core	Study completion
Visit Number			**13**	**14**	**15**	**16**	**17**	**776**	**18**	**19**	**20**	**777**	**779**
Day			**183**	**197**	**211**	**225**	**239**		**253**	**281**	**309**	**337**	**30 days from last dose**
week			**26**	**28**	**30**	**32**	**34**		**36**	**40**	**44**	**48**	
Plasma ACTH, serum cortisol	D	7.2.2.4.6.	x		x		x		x	x	x	x	x
Serum 11-deoxycortisol	D	7.2.2.4.6.					x					x	x
Serum aldosterone	D	7.2.2.4.6.					x					x	x
Renin	D	7.2.2.4.6.					x					x	x
[redacted]													
Serum 11-Deoxycorticosterone	D	7.2.2.4.6.					x					x	x
Fasting serum Insulin and plasma glucose	D	7.2.2.4.7.					x					x	x
HbA1C	D	7.2.2.4.7.					x					x	x
Safety													
Adverse Events	D	8.1.	As required										
12 Lead safety ECG assessment	D	7.2.2.6.2.	x		x		x		x	x	x		x
12-Lead 24-hour Holter ECG recording	D	7.2.2.6.1.										x	
Imaging													
Pituitary MRI (or CT)	D	7.2.2.5.										x	
Photography	D	7.2.1.2.					x					x	
DXA scan	D	7.2.1.3.										x	
Patient Reported Outcomes													
HRQoL EQ-5D-5L, CushingQoL, Beck Depression Inventory	D	7.2.6.	x		x		x					x	
Study Drug administration	D	6.1.1.	continuous b.i.d. dosing										
PK sampling	D	7.2.3.	x		x		x		x	x	x	x	
Serum cortisol, salivary cortisol, plasma ACTH (China subset)	D	7.2.2.4.6.	x		x		x		x	x	x	x	

	Category	Protocol Section	Randomized Withdrawal period					EOT randomized withdrawal period	Open Label period			EOT core	Study completion
Visit Number			**13**	**14**	**15**	**16**	**17**	**776**	**18**	**19**	**20**	**777**	**779**
Day			**183**	**197**	**211**	**225**	**239**		**253**	**281**	**309**	**337**	**30 days from last dose**
week			**26**	**28**	**30**	**32**	**34**		**36**	**40**	**44**	**48**	
Serum cortisol (Extensive PK subset)	D	7.2.2.4.6.	x		x		x		x	x	x	x	
[redacted]													
End of randomized withdrawal period form	D							x					
End of treatment core form	D											x	
End of study form	D												x

Table 7-4 Visit evaluation schedule – Optional Extension period (Year 1)

	Category	Protocol Section	Extension								
Visit Number			**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**
Day			**337**	**365**	**393**	**421**	**449**	**477**	**505**	**589**	**673**
week			**48**	**52**	**56**	**60**	**64**	**68**	**72**	**84**	**96**
Obtain Informed consent	S		x								
IWRS/IRT	S		x	x	x	x	x	x	x	x	x
Prior/concomitant medication	D	7.1.1.3.	As required								
Physical examination	S	7.2.2.1.		x	x	x	x	x	x	x	x
Body weight	D	7.2.2.3.		x	x	x	x	x	x	x	x
Waist circumference	D	7.2.2.3.		x	x	x	x	x	x	x	x
Vital signs											
Body temperature	D	7.2.2.2.		x	x	x	x	x	x	x	x
Blood pressure/Pulse rate	D	7.2.2.2.		x	x	x	x	x	x	x	x
Laboratory assessments											
Hematology	D	7.2.2.4.1.		x	x	x	x	x	x	x	x
Chemistry - full	D	7.2.2.4.2.		x	x	x	x	x	x	x	x
Thyroid Panel	D	7.2.2.4.5.				x			x		x
Luteinizing Hormone (LH) and Follicle stimulating hormone (FSH)	D	7.2.2.4.6.				x			x		x
Coagulation	D	7.2.2.4.4.				x			x	x	x
Urinalysis	D	7.2.2.4.3.				x			x	x	x
Pregnancy test (urine)	D	7.2.2.4.8.		x	x	x	x	x	x	x	x
Efficacy Assessment											
24-hour Urinary Free Cortisol and creatinine	D	7.2.1.1.				x			x	x	x
Serum testosterone and estradiol	D	7.2.2.4.6.				x			x	x	x
Plasma ACTH, serum cortisol	D	7.2.2.4.6.				x			x	x	x
Serum 11-deoxycortisol	D	7.2.2.4.6.				x			x	x	x
Serum Androstenedione, DHEAS, Estrone	D	7.2.2.4.6.				x			x	x	x

	Category	Protocol Section	Extension								
Visit Number			**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**
Day			**337**	**365**	**393**	**421**	**449**	**477**	**505**	**589**	**673**
week			**48**	**52**	**56**	**60**	**64**	**68**	**72**	**84**	**96**
Serum aldosterone	D	7.2.2.4.6.				x			x	x	x
Renin	D	7.2.2.4.6.				x			x	x	x
[redacted]											
Serum11-Deoxycorticosterone	D	7.2.2.4.6.				x			x	x	x
Fasting serum Insulin and plasma glucose	D	7.2.2.4.7.				x			x	x	x
HbA1C	D	7.2.2.4.7.				x			x	x	x
Safety											
Adverse Events	D	8.1.	As required								
12 Lead safety ECG assessment	D	7.2.2.6.2.	x			x			x	x	x
24-hour Holter ECG recording	D	7.2.2.6.1.							x		
Imaging											
Pituitary MRI (or CT)	D	7.2.2.5.							x		
Photography	D	7.2.1.2.							x		
DXA scan	D	7.2.1.3.									
Patient Reported Outcomes											
HRQoL EQ-5D-5L, CushingQoL, Beck Depression Inventory	D	7.2.6.							x		x
Study Drug administration	D	6.1.1.	continuous b.i.d. dosing								

Table 7-5 Visit evaluation schedule – Optional Extension period (After Year 1)

	Category	Protocol Section	Extension					EOT Extension	Study completion
							Subsequent Visits		
Visit Number			**30**	**31**	**32**	**33**	**34, 35, 36, …**	**778**	**779**
Day			**757**	**841**	**925**	**1009**	**1093, 1177, 1261, …**	**28 days since last visit**	**30 days from last dose**
week			**108**	**120**	**132**	**144**	**156, 168, 180, …**	**4 weeks since last visit**	
Obtain Informed consent	S								
IWRS/IRT	S		x	x	x	x	x	x	x
Prior/concomitant medication	D	7.1.1.3.	As required						
Physical examination	S	7.2.2.1.	x	x	x	x	x	x	x
Body weight	D	7.2.2.3.	x	x	x	x		x	x
Waist circumference	D	7.2.2.3.	x	x	x	x		x	x
Vital signs									
Body temperature	D	7.2.2.2.	x	x	x	x	x	x	x
Blood pressure/Pulse rate	D	7.2.2.2.	x	x	x	x		x	x
Laboratory assessments									
Hematology	D	7.2.2.4.1.	x	x	x	x	**Same Extension assessments will be performed with same frequency.**	x	x
Chemistry - full	D	7.2.2.4.2.	x	x	x	x		x	x
Thyroid Panel	D	7.2.2.4.5.		x		x			x
Luteinizing Hormone (LH) and Follicle stimulating hormone (FSH)	D	7.2.2.4.6.		x		x			x
Coagulation	D	7.2.2.4.4.	x	x	x	x		x	x
Urinalysis	D	7.2.2.4.3.	x	x	x	x		x	x
Pregnancy test (urine)	D	7.2.2.4.8.	x	x	x	x		x	x

	Category	Protocol Section	Extension					EOT Extension	Study completion
							Subsequent Visits		
Visit Number			**30**	**31**	**32**	**33**	**34, 35, 36, …**	**778**	**779**
Day			**757**	**841**	**925**	**1009**	**1093, 1177, 1261, …**	**28 days since last visit**	**30 days from last dose**
week			**108**	**120**	**132**	**144**	**156, 168, 180, …**	**4 weeks since last visit**	
Efficacy Assessment									
24-hour Urinary Free Cortisol and creatinine	D	7.2.1.1.	x	x	x	x	**Same Extension assessments will be performed with same frequency.**	x	x
Serum testosterone and estradiol	D	7.2.2.4.6.		x		x		x	x
Plasma ACTH, serum cortisol	D	7.2.2.4.6.	x	x	x	x		x	x
Serum 11-deoxycortisol	D	7.2.2.4.6.		x		x			x
Serum Androstenedione, DHEAS, Estrone	D	7.2.2.4.6.		x		x			x
Serum aldosterone	D	7.2.2.4.6.		x		x			x
Renin	D	7.2.2.4.6.		x		x			x
[redacted]									
Serum11-Deoxycorticosterone	D	7.2.2.4.6.	x	x	x	x			x
Fasting serum Insulin and plasma glucose	D	7.2.2.4.7.		x		x			x
HbA1C	D	7.2.2.4.7.		x		x			x
Safety									
Adverse Events	D	8.1.	As required						
12 Lead safety ECG assessment	D	7.2.2.6.2.	x	x	x	x	**Same Extension assessments will be performed with same frequency.**	x	x
24-hour Holter ECG recording	D	7.2.2.6.1.		x				x	
Imaging									
Pituitary MRI (or CT)	D	7.2.2.5.		x			**Same Extension assessments will be performed with same frequency.**	x	
Photography	D	7.2.1.2.						x	
DXA scan	D	7.2.1.3.						x	

	Category	Protocol Section	Extension					EOT Extension	Study completion
							Subsequent Visits		
Visit Number			**30**	**31**	**32**	**33**	**34, 35, 36, …**	**778**	**779**
Day			**757**	**841**	**925**	**1009**	**1093, 1177, 1261, …**	**28 days since last visit**	**30 days from last dose**
week			**108**	**120**	**132**	**144**	**156, 168, 180, …**	**4 weeks since last visit**	
Patient Reported Outcomes									
HRQoL EQ-5D-5L, CushingQoL, Beck Depression Inventory	D	7.2.6.						x	
Study Drug administration	D	6.1.1.	continuous b.i.d. dosing						
End of treatment extension form	D							x	
End of study form	D								x

7.1.1 Screening

Written main informed consent must be obtained before any study specific assessments are performed.

The screening assessments must be performed within 35 days before planned patient's eligibility confirmation and before the start of the first study drug dose of LCI699 at day 1.

For patients who are on a medication requiring a >4 week washout, consideration can be given to switching them to a medication with a shorter washout (1 week) until the last part of the washout.

Based on the central laboratory turnaround time, it is highly recommended to send the three 24-hour Urinary Free Cortisol samples to the central Laboratory at least 14 days prior to day 1 in order to ensure that sufficient time is allowed for central laboratory results to become available.

Eligibility is assessed based on the screening results only collected at the screening visit, unless specified otherwise as per the Inclusion/Exclusion criteria. For details, refer to Section 5.2 and Section 5.3.

For laboratory evaluations used to determine eligibility, a repeated evaluation within the screening window is permitted for screening results out of the defined range. If the repeated laboratory result meets the criteria, that result may be used to determine eligibility. If the repeated laboratory result does not meet the criteria, the patient will be considered a screening failure. In this case, the patient will not be required to sign another ICF.

A new ICF will need to be signed if the investigator chooses to re-screen the patient after a patient has screen failed. The rescreening should be documented in the source files and re-registered in IRT using the same Patient Number.

If the rescreening occurs within 60 days of the end of the original screening period, the following procedures do not have to be repeated: pituitary MRI, photography and DXA scan and all other assessments must be repeated.

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

An individual patient may only be rescreened once for the study. Once the number of patients screened and enrolled is likely to ensure target enrollment, the Sponsor may close the study to further screening. In this case the patients who screen failed will not be permitted to re-screen. For details of assessments, refer to Table 7-1.

[redacted]

7.1.1.1 Eligibility screening

While the investigator is responsible to ensure that each patient meets all inclusion/exclusion criteria prior to randomization, a subset of those criteria have been identified as key eligibility criteria and will also be verified by the sponsor through IRT prior to permitting the patient to be randomization. Patient's eligibility is checked in IRT. The eligibility checklist form must be completed in IRT by the investigator or designee at day 1 prior to starting the treatment phase

and receiving the first dose of study drug (LCI699). Verification of all eligibility criteria must be done prior to contacting IRT. After the eligibility has been checked in IRT and confirmed that the patient is eligible for the trial, then the patient can be enrolled into the treatment phase of the study.

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

7.1.1.2 Information to be collected on screening failures

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the Screening Failure Log, and each patient's demographic information will be recorded on the Demography CRF page.

No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a Serious Adverse Event during the Screening Phase (see Section 8.2 for SAE reporting details).

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

7.1.1.3 Patient demographics and other baseline characteristics

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

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

Furthermore the following assessments will be performed:

- Physical Examination (see Section 7.2.2.1),
- Vital signs including blood pressure and pulse (see Section 7.2.2.2),
- Patient quality of life questionnaires (CushingQoL, Beck Depression Inventory, HRQoL EQ-5D-5L) (see Section 7.2.6),
- ECG and 24-hour Holter (see Section 7.2.2.6),
- MRI, photography and DXA Imaging (see Section 7.2.2.5, Section 7.2.1.2 and Section 7.2.1.3),

- Laboratory evaluations (e.g., hematology, biochemistry, thyroid panel, coagulation, lipase, glycosylated hemoglobin (HbA1c), fasting insulin and plasma glucose, urinalysis, 24-hour Urinary Free Cortisol and creatinine, testosterone and estradiol, LH and FSH, plasma ACTH, cortisol, 11-deoxycortisol, renin, serum aldosterone, [redacted], serum 11-deoxycorticosterone, serum androstenedione, DHEAS, estrone) (see Section 7.2.2.4),
- Serum pregnancy (see Section 7.2.2.4.8).

7.1.2 Run-in period

Although there is no Run-in period, washout requirements as described in Inclusion criteria (Section 5.2) must be followed.

7.1.3 Treatment period

Treatment period is divided in 4 study periods as described in Section 4.1. Patients should be seen for all visits on the designated day with a visit window of ± 3 days and in a fasting state.

During study period 1 (Week 1 to 12), patients will come to the site every 2 weeks. Between visits, they may be contacted by the Investigator/designee in order to increase or decrease the study drug dose based on UFC results from previous visit.

During study period 2 (Week 13 to 24), patients will come to site every 4 weeks. Although study drug dose usually remains stable during this period, adjustment may be needed based on mUFC results and for safety.

Blood samples will be collected for all patients for sparse PK purpose throughout the core study (week 1 – 48). Pharmacokinetic blood collection for a subset of approximately 20 patients will be carried out for extensive PK assessment.

During study period 3 (Week 26 to 34), patients will either continue LCI699 open label if they are not randomized and will have visits every 4 weeks; or will be randomized to one of the 2 arms and will come to site every 2 weeks.

During study period 4 (Week 35 to 48), patients will come to site every 4 weeks.

During study periods 3 and 4, patients are also allowed to have unscheduled visits at any time if they report symptoms of hypercortisolism and have their dose adjusted accordingly.

For details of assessments, please refer to Table 7-1 to Table 7-5 depending on study period.

7.1.4 End of treatment visit including study completion and premature withdrawal

Patients who discontinue study treatment before visit 777 (if patient is in the core phase of the study) or 778 (if patient is in the extension phase of the study), should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the EOT visit will be performed (Table 7-1, Table 7-3 or Table 7-5) with the following exceptions:

- Patients discontinuing treatment prior to the Week 36 visit do not need to have an EOT core DXA scan

- Patients discontinuing prior to the Week 12 visit or between the Week 24 and Week 36 visits do not need to have an EOT core pituitary MRI (or CT) (i.e. scans are needed if patients discontinue within the 12 week period prior to the Week 24 and Week 48 visits).
- Patients discontinuing or completing extension phase within 36 weeks since their last pituitary MRI (or CT) or DXA scan do not need to have an EOT extension pituitary MRI (or CT) or DXA scans.

An End of Treatment Phase Disposition CRF page should be completed, giving the date and reason for stopping the study treatment. At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 30 days following the last dose of study treatment (Visit 779).

If a patient withdraws or discontinues from the study prematurely, an unscheduled PK sample should be taken, and the sample should be recorded in the "Unscheduled PK" CRF page.

7.1.5 Discontinuation of study treatment

Patients may voluntarily discontinue from the study treatment for any reason at any time. If a patient decides to discontinue from the study treatment, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information in the patient's chart and on the appropriate CRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

- The investigator should discontinue study treatment for a given patient if, on balance, he/she believes that continuation would be detrimental to the patient's well-being.

Study treatment must be discontinued under the following circumstances:

- Emergence of the following adverse events:
  - hypertension defined as office mean sitting systolic BP > 180 mmHg or mean sitting diastolic BP > 110 mmHg (confirmed and persistent*).
- Any of the following laboratory abnormalities (confirmed):
  - hyperkalemia (serum potassium > 6.0 mmol/L).
  - hypokalemia (serum potassium < 2.8 mmol/L).
- Any of the following laboratory abnormalities (confirmed and persistent*):
  - hyperkalemia (serum potassium > 5.5 mmol/L).
  - hypokalemia (serum potassium < 3.0 mmol/L).
  - hyponatremia (serum sodium < 130 mmol/L).
  - AST or ALT >3.0 x ULN combined with total bilirubin >2.0 x ULN without evidence of cholestasis
- QTcF > 500 msec, if confirmed by a cardiologist (see Section 7.2.2.7).

QTcF > 480 msec, if the investigator determines it is no longer safe for the patient to continue in the study, based on ECGs, cardiac examination, and recommendation from a cardiologist (see Section 7.2.2.7).

- QTcF increase > 60 msec from pre-first dose baseline measurement.

- Mean increase in QTcF > 30 ms from the mean baseline value at 1.5 hour post-first dose or mean QTcF > 480 ms at day 1 (see Section 7.2.2.7).
- Pituitary tumor growth, if the tumor is < 2mm from the optic chiasm, or symptoms of actual compression of the optic chiasm emerge (visual field loss, cranial nerve palsies, diplopia) confirmed by MRI of the pituitary.

* Persistent is defined as unresolved with LCI699 dose and/or other concomitant medication changes.

- Pregnancy.
- Use of prohibited concomitant medications (see Section 6.4.2).
- Any other protocol deviation that results in a significant risk to the patient's safety.

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

Patients who discontinue study treatment should NOT automatically be considered withdrawn from the study. They should return for the assessments indicated in Section 7.2. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, email, letter) should be made to contact them as specified in Section 7.1.8.

The investigator must also contact the IRT to register the patient's discontinuation from study treatment.

7.1.5.1 Replacement policy

Not applicable.

7.1.6 Withdrawal of informed consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the patient's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

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

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a patient's samples until their time of withdrawal) according to applicable law.

For United States and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For European Union and RoW (Rest of World, i.e. all countries except the United States, Japan and the member states of the European Union): All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

7.1.7 Follow up for safety evaluations

All patients must have safety evaluations for 30 days after the last dose of study treatment.

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

7.1.8 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow up should be recorded as such on the appropriate Study phase completion CRF.

7.2 Assessment types.

7.2.1 Efficacy assessments

Table 7-6 Imaging and disease assessment collection plan

Procedure	Screening/Baseline	During Treatment/Extension
24-hour urine to test for Urine Free Cortisol and creatinine	Mandated at screening and baseline	Mandated, every 2 or 4 weeks depending on study period in core phase and every 12 weeks in extension phase. Three 24-hour samples at each time point
Photography	Mandated at baseline	Mandated at week 12, 24, 34 and 48 in core phase, week 72 and EOT in extension
DXA scan	Mandated at baseline	Mandated at end of treatment core and end of treatment extension

7.2.1.1 Urinary Free Cortisol

The primary efficacy parameter will be Urinary Free Cortisol (UFC) and will be assessed using a central laboratory. UFC will be measured in three 24-hour urine samples. The three samples will be averaged to obtain the mean UFC (mUFC) level.

Throughout the study, patients will collect three 24-hour UFC samples according to the Table 7-1 to Table 7-5:

Screening: three 24-hour UFC samples should be collected and sent to central laboratory at least 14 days prior to day 1 in order to ensure that sufficient time is allowed for central laboratory results to become available. These samples will be used to assess eligibility of the patient. A repeated evaluation within the screening window is permitted for screening results out of the defined range. If the repeated laboratory result meets the criteria, that result may be used to determine eligibility. If the repeated laboratory result does not meet the criteria, the patient will be considered a screening failure.

Baseline: another three 24-hour UFC samples will be collected within 7 days prior to first day of treatment to serve as baseline value.

Treatment period: patient will collect three 24-hour UFC samples within 7 days prior to the next visit and with the last urine sample preferably collected the day prior to the visit at site as defined in Table 7-1 during study periods 1 and 2; as defined in Table 7-2 (for randomized patients) or Table 7-3 (for non-randomized patients) during study periods 3 and 4; and as defined in Table 7-4 and Table 7-5 during extension period. Please refer to Section 4.1 for complete description of study design.

During study periods 3 and 4, patients are also allowed to have unscheduled visits at any time if they report symptoms of hypercortisolism.

7.2.1.2 Photographic assessments of physical findings

The following clinical signs (physical findings) of Cushing's disease will be assessed at time points defined in Table 7-1 to Table 7-5 : facial rubor, hirsutism (females only), striae, supraclavicular and dorsal fat pads, proximal muscle wasting (atrophy), central (abdominal) obesity, and ecchymoses (bruising). These clinical signs are to be rated on a semi-quantitative scale as follows: 0=absent; 1=mild; 2=moderate; and 3=severe. The photographs will be reviewed locally by the investigator and used for analysis. Photographs will be centrally collected and checked for quality by an imaging vendor. The quality checks will be detailed in the vendor manual.

Two photographs, one frontal and one lateral from the shoulders up will be taken to assess facial plethora (rubor), supraclavicular and dorsal fat pads. Two photographs, frontal and dorsal of the trunk with patient in standing position will be taken to assess hirsutism (females only), striae, proximal muscle wasting (atrophy), central (abdominal) obesity, and ecchymoses (bruising). In order to maintain confidentiality, photographs will not be published without the explicit written consent of the patient.

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

7.2.1.3 Bone mineral density assessments

Bone mineral density of the lumbar vertebrae (L1-L4 or L2-L4, depending upon manufacturer) and left total hip are to be measured using Lunar or Hologic DXA (dual-energy X-ray

absorptiometry) Instruments. A patient should be scanned on the same DXA instrument throughout the study. If a scan of the left femur is not possible, then the right femur can be used which is then to be used consistently throughout the study. Patients are to be positioned and scanning is to be performed according to the instructions from the manufacturer. Detailed instructions on scanning methods, calibration of individual DXA machines and across DXA machines at different sites will be provided in a DXA manual. The BMD results should be reported in actual density (gm/cm^2) and standardized against the peak bone mass in a healthy young adult population (BMD T-score). BMD results will be reviewed centrally by the imaging vendor. This assessment will be done as defined in Table 7-1 to Table 7-5.

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

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing physical examination, vital signs, laboratory evaluations, radiological examinations, radiological assessments, cardiac assessments, as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 8.

7.2.2.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, and extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and/or pelvic exams may be performed. This will be conducted at visits according to Table 7-1 to Table 7-5.

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

7.2.2.2 Vital signs

Vital signs include body temperature, blood pressure and pulse measurements, and will be assessed according to Table 7-1 to Table 7-5.

After the patient has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using an automated validated device, with an appropriately sized cuff. The repeat sitting measurements will be made at 1 - 2 minute intervals and the three measurements will be reported. An appropriately sized cuff should be used.

7.2.2.3 Height, weight and waist circumference

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured. Body height will be measured at screening and body weight and waist circumference will be measured at visits according to Table 7-1 to Table 7-5.

To measure the waist circumference, patients should remove clothing from around the waist to ensure the measuring tape is correctly positioned. Using e.g. a cosmetic pencil, make a mark at

the "natural waist" midway between the palpated iliac crest and the palpated lowest rib margin in the left and right mid-axillary lines. Place the non-stretchable tape evenly around the natural waist covering the left and right natural waist marks. The measurement scale should face outward, and there should be no twists in the tape. Ensure that the tape is just touching the skin but not compressing the soft tissue. Instruct patients to stand erect with abdomen relaxed, arms at sides, feet together, and weight divided equally over both legs.

7.2.2.4 Laboratory evaluations

Clinical laboratory analyses (hematology, chemistry (full or partial), coagulation, urinalysis, thyroid panel and additional tests mentioned in Table 7-7 below) are to be performed by the central laboratory. Visit windows of +/- 3 days are allowed.

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

Table 7-7 Central clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, RBC Morphology with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)
Chemistry - full	Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Bicarbonate, Glucose, Calcium, Chloride, Creatinine, Creatine kinase, GGT, Lactate dehydrogenase (LDH), inorganic phosphorus, lipase, amylase, magnesium, potassium, sodium, Total Bilirubin (and Direct Bilirubin, Indirect Bilirubin if total Bilirubin is above 1.5 times the upper limit of normal), Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid
Chemistry - partial	Sodium, potassium, chloride, bicarbonate, Blood Urea Nitrogen (BUN) or Urea, creatinine, glucose, calcium, magnesium
Urinalysis	Macroscopic Panel (Dipstick) (Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, pH, Protein, Specific Gravity,)
Coagulation	Prothrombin time (PT), Activated partial thromboplastin time (APTT)
Thyroid Panel	Serum TSH, free T4
Additional tests	Pregnancy test: serum (central laboratory testing) and urine dipstick (local laboratory testing) Serum testosterone and estradiol Plasma ACTH, serum cortisol, serum 11-deoxycortisol Serum aldosterone Renin [redacted] Serum 11-Deoxycorticosterone Fasting serum insulin and plasma glucose HbA1C LH, FSH Serum Androstenedione, DHEAS, Estrone Serum cortisol [redacted] (Extensive PK subset) (See Section 7.2.2.4.6)

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

7.2.2.4.1 Hematology

Hematology tests are to be performed by the central laboratory according to the schedule of assessments and collection plan outlined respectively in Table 7-1 to Table 7-5. The Hematology panel includes hematocrit, hemoglobin, platelets, red blood cells (RBC), white blood cells, RBC morphology with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils).

7.2.2.4.2 Clinical chemistry

Chemistry tests are to be performed by the central laboratory according to the schedule of assessments and collection plan outlined respectively in Table 7-1 to Table 7-5.

The full Chemistry panel includes albumin, alkaline phosphatase, ALT (SGPT), AST (SGOT), bicarbonate, glucose, calcium, chloride, creatinine, creatine kinase, GGT, LDH, inorganic phosphorus, lipase, amylase, magnesium, potassium, sodium, total bilirubin (and direct bilirubin, indirect bilirubin, total cholesterol, LDL, HDL, total protein, triglycerides, Blood Urea Nitrogen (BUN) or urea, uric acid.

The partial Chemistry panel includes sodium, potassium, chloride, bicarbonate, Blood Urea Nitrogen (BUN) or urea, creatinine, glucose, calcium, magnesium.

7.2.2.4.3 Urinalysis

Urinalysis tests are to be performed according to the schedule of assessments and collection plan outlined respectively in Table 7-1 to Table 7-5.

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

A semi-quantitative "dipstick" evaluation for the following parameters will be performed: specific gravity, pH, glucose, protein, bilirubin, ketones, leukocytes esterase and blood.

7.2.2.4.4 Coagulation

Prothrombin time (PT), Activated Partial Thromboplastin Time (APTT) will be assessed by the central laboratory according to Table 7-1 to Table 7-5.

7.2.2.4.5 Thyroid panel

Serum Thyroid Stimulating Hormone (TSH) and free T4 will be assessed by the central laboratory according to Table 7-1 to Table 7-5.

7.2.2.4.6 Additional hormones

Serum testosterone and estradiol, luteinizing hormone (LH) and follicle stimulating hormone (FSH), plasma ACTH, serum cortisol, serum 11-deoxycortisol, renin, serum aldosterone, [redacted], serum androstenedione, DHEAS, estrone and serum

11-deoxycorticosterone will be assessed by the central laboratory according to Table 7-1 to Table 7-5.

For the subset of patients (n~20) participating in extensive PK assessment (See Section 7.2.3), serum and salivary cortisol will also be collected at the same time as PK samples; additional salivary cortisol samples will be taken the day prior to the visit at 8 am, 12 pm, 6 pm and midnight, all with a window of +/- 1 hour. If LCI administration was interrupted prior to a planned visit and no study treatment is administered on the day of the planned visit, sampling for serum and salivary cortisol will not be required, similarly as the PK sampling.

For the subset of Chinese patients with extensive PK sampling, serum and salivary cortisol and plasma ACTH will be collected at the same time as PK samples; additional salivary cortisol samples will be taken the day prior to the visit at 8 am, 12 pm noon, 6 pm and midnight, all with a window of +/- 1 hour. Additionally at baseline (Visit 2) these patients will undergo sampling for plasma ACTH and serum cortisol at 8 am, 12 pm noon, 4 pm and 8 pm. If LCI administration was interrupted prior to a planned visit and no study treatment is administered on the day of the planned visit, sampling for serum, salivary cortisol and plasma ACTH will not be required, similarly as the PK sampling.

Collection times for serum cortisol, salivary cortisol and plasma ACTH (when applicable) are identical to the PK collection schedule (see Section 7.2.3, Table 7-11) with the exception of the additional salivary and serum cortisol and plasma ACTH samples taken prior to the visit.

7.2.2.4.7 Other laboratory parameters

Serum fasting insulin and plasma fasting glucose, HbA1C will be assessed by the central laboratory according to Table 7-1 to Table 7-5.

7.2.2.4.8 Pregnancy and assessments of fertility

Serum pregnancy tests will be performed at screening, baseline. Urine or serum pregnancy testing will be performed as indicated in Table 7-1 to Table 7-5.

If a urine pregnancy test is performed and is found to be positive, this will require immediate interruption of study drug until serum β-hCG is performed and found to be negative. If positive, the patient must be discontinued from the trial.

When performed at screening, the result of this test must be received before the patient may be dosed.

7.2.2.5 Radiological examinations

Table 7-8 Imaging assessment collection plan

Procedure	Screening/Baseline	During Treatment/Extension
Pituitary MRI with gadolinium enhancement	Mandated at baseline	Mandated at Week 24, 48,72, 120, subsequently at the same frequency and at EOT extension

Pituitary MRI scanning with gadolinium enhancement will be performed at visits according to Table 7-1 to Table 7-5. These will be assessed centrally by the imaging vendor to screen for pituitary enlargement either by tumor volume or maximum dimension of tumor. If MRI scan

with intravenous contrast (gadolinium) is contraindicated for a patient, then a non-contrast MRI scan should be performed. If the MRI cannot be performed at all, then a CT of the pituitary (with i.v. contrast if not contraindicated) may be performed. Regardless of imaging type, all regularly scheduled pituitary imaging will be centrally reviewed by the imaging vendor for consistency in the measurement of dimensions. The modality (MRI/CT) should remain consistent to that used at baseline unless there is a development of a contraindication. The central reading at each time point will include the assessment of invasiveness of the pituitary tumor into surrounding structures, and any new finding of measurable pituitary tumor in a patient with no measureable tumor at previous scans. Please see the study imaging manual for further information.

7.2.2.6 Cardiac assessments

Cardiac monitoring will include 12-lead Safety ECGs, which are the primary assessment of safety at study visits, and 24-hour continuous 12-lead Holter recordings, which provide large amounts of additional ECG data with central reading, but are not intended to provide real-time assessment of cardiac intervals and cardiac rhythm.

Table 7-9 ECG collection plan

Week	Day	Time	ECG Type	Central or Local
-5 to -2	-35 to -8	Pre-dose	12 Lead	Local
-1	-7 to -1	Pre-dose	12 Lead	Local
-1	-7 to -1	24-hour	24-hour Holter	Central
0	1	Pre-dose	12 Lead	Local
0, 2, 4, 6, 8, 10, 12, 16, 20, 24	1, 15, 29, 43, 57, 71, 85, 113, 141, 169	Post-dose 1.5 hours	12 Lead	Local
Randomized patients: 26, 28, 30, 32, 34, 36, 40, 44	183, 197, 211, 225, 239, 253, 281, 309	Post-dose 1.5 hours	12 Lead	Local
Non randomized patients: 26, 30, 34, 36, 40, 44	183, 211, 239, 253, 281, 309	Post-dose 1.5 hours	12 Lead	Local
2, 12, 24, 48	15, 85, 169, 337	24-hour	24-hour Holter	Central
Optional Extension: 48, 60, 72, 84, 96, 108, 120, 132, 144, subsequently at the same frequency and EOT extension	337, 421, 505, 589, 673, 757, 841, 925, 1009, subsequently at the same frequency and EOT extension	Post-dose 1.5 hours	12 Lead	Local
Optional Extension: 72, 120, subsequently at the same frequency and EOT extension	505, 841, subsequently at the same frequency and EOT Extension	24-hour	24-hour Holter	Central
Study completion	30 days from last dose	N/A	12 Lead	Local
Unscheduled assessment		Anytime	12 Lead	Local

7.2.2.6.1 24-hour Holter electrocardiogram

Twenty-four hour continuous 12-lead Holter recording with central reading of data are done on each patient according to the Table 7-1 to Table 7-5 and Table 7-9.

7.2.2.6.2 Electrocardiogram (ECG)

Twelve-lead safety ECGs are collected at the study sites according to Table 7-1 to Table 7-3 and Table 7-9. At each visit when a study drug dose is administered, the safety ECG should be collected at 1.5 hours post-dose (approximately at the time of Cmax). If the patient chooses to enroll in the Extension Study, 12-lead safety ECGs will also be done according to the Table 7-4 and Table 7-5, and the timing will also be 1.5 hours post-dose if study drug is administered.

Twelve-lead safety ECGs are collected at the study site using ECG equipment provided by vendor. This ECG must be read on site by a qualified physician (e.g., the investigator, or another qualified physician such as a consulting cardiologist) at the time they are collected and documented on the ECG CRF.

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

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

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

The CRF will contain:

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

The Fridericia QT formula (QTcF) to correct for variations in heart rate should be used for clinical decisions.

The purpose of the safety ECG is to identify patients with clinically significant ECG abnormalities. On the day of the first study drug administration (day 1), pre-dose ECGs must be done in triplicate. The mean of the QTcF from these 3 tracings is used as the baseline QTcF to be compared with subsequent ECGs.

ECGs with clinically significant abnormalities should be reported on the CRF. The overall interpretation will be collected with a Yes/No statement to confirm if any clinically significant abnormalities are present which need to be specified further.

A “notable ECG abnormality” is defined as:

- Day 1 only: an increase in QTcF > 30 msec at 1.5 hours post-dose, compared to the mean pre-dose baseline QTcF from the same day
- QTcF > 480 msec with acute cardiovascular risk, as assessed by a consulting cardiologist
- Any QTcF > 500 msec, confirmed by a consulting cardiologist
- QTcF increase > 60 msec from baseline.

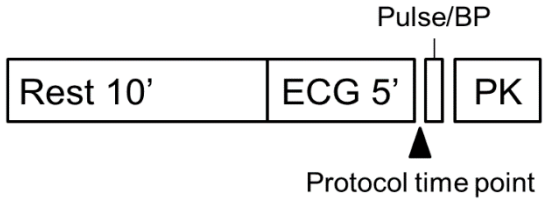
Notable ECG abnormalities should be recorded on the Adverse Events CRF page. If there is a notable abnormality, then a cardiology consult should be called, and the Novartis Medical Monitor for this trial notified of the event.

For any ECGs with clinically significant or notable ECG abnormalities, two additional 12-lead ECGs should be performed to confirm the safety finding and the triplicate ECGs collected should be transferred for central review.

ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline.

The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and then blood sampling for LCI699 pharmacokinetic (PK) assessment (Figure 7-1). ECG procedure may also be performed 30 minutes after PK sampling.

Figure 7-1 Sequence of cardiovascular data collection



Original ECG tracings, appropriately signed, will be archived at study site.

7.2.2.7 QT monitoring

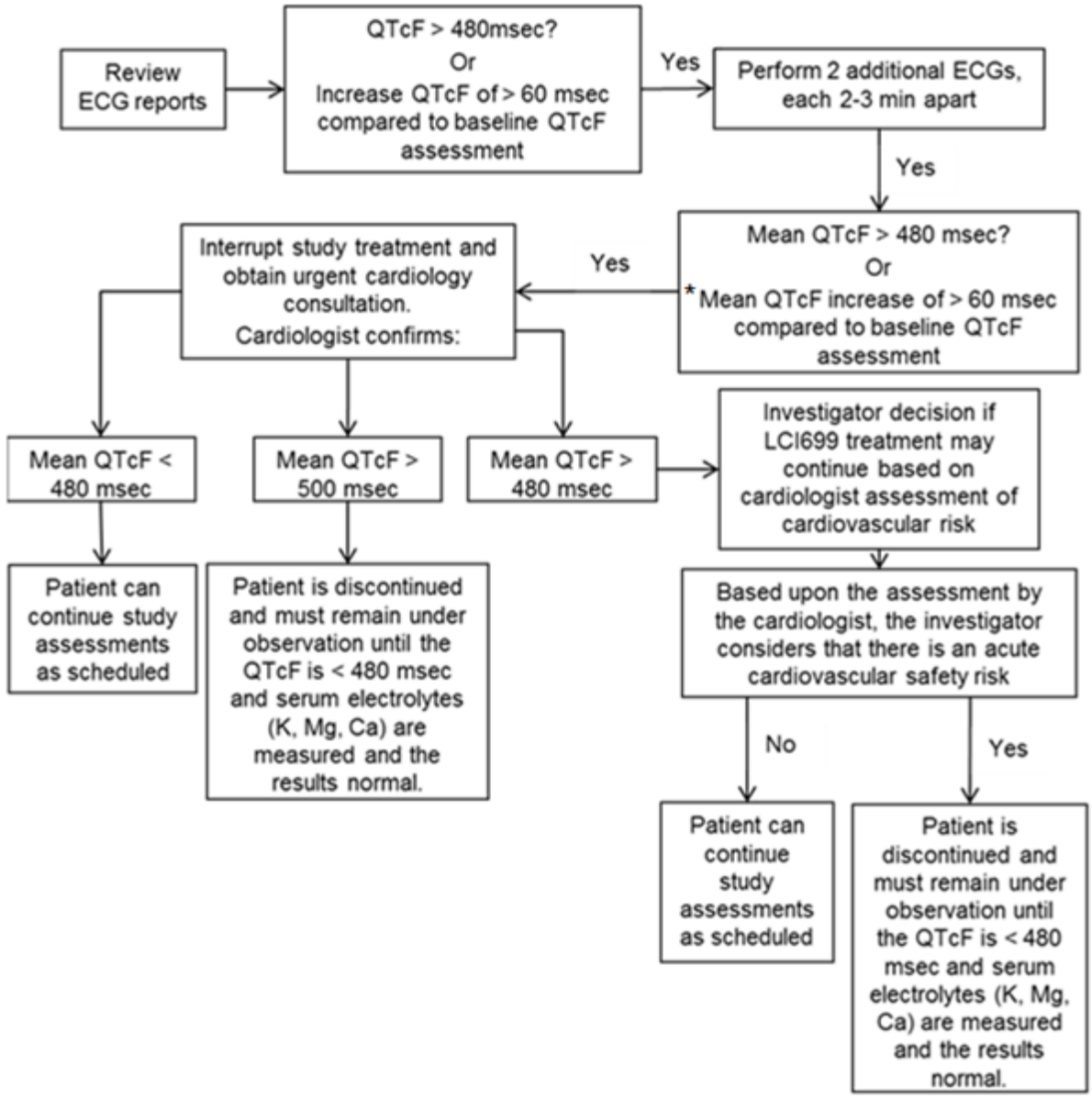
QT monitoring will occur as follows:

- On the first day of the first administration of LCI699 (day 1), pre-dose baseline ECGs must be done in triplicate. The mean of the QTcF values from these three ECG tracings is used to determine the mean baseline QTcF.
- On day 1, if the safety ECG (1.5 hours post-first dose of LCI) shows a mean increase in QTcF > 30 ms from the mean baseline value, or the mean QTcF is > 480 ms, then the patient must be discontinued from the study drug according to the discontinuation procedure described in Section 7.1.7 and an unscheduled triplicate ECGs collected at approximately 1-2 hours and a PK sample collected. The patient must remain under observation until the QTcF is < 480 msec and serum electrolytes, calcium, and magnesium are measured and the results normal.
- If at any follow up visit, a QTcF > 480 msec is observed or an increase of the QTcF of >60 msec compared to baseline QTcF assessment, then two additional ECGs, each 2-3 minutes apart, need to be taken after the initial ECG. The mean QTcF from the triplicate ECGs will be determined. If the mean QTcF is > 480 msec or the mean QTcF increase is >60 msec compared to baseline, the patient has to interrupt study treatment while an urgent cardiology consultation is obtained to re-evaluate the ECG and perform a clinical consultation. If immediate treatment is required for patient safety, this should be initiated at the study site without delay and without waiting for confirmation by a cardiologist.

Based on the cardiologist consultation, the following should occur:

- If a mean QTcF > 480 msec is NOT confirmed, no further action needs to be taken.If the cardiologist confirms a mean QTcF > 500 msec, the patient has to discontinue according to the discontinuation procedure described in Section 7.1.7 and an unscheduled PK sample collected. The patient must remain under observation until the QTcF is < 480 msec and serum electrolytes, calcium, and magnesium are measured and the results normal. This observation may be done at the site, in an Emergency Room, or a cardiology clinic, as appropriate and depending upon local resources.
  a. If the cardiologist confirms that QTcF > 480 msec, LCI699 treatment is temporarily interrupted and a thorough evaluation is performed to assess the patient for acute cardiovascular risk, and for possible underlying heart disease that needs additional evaluation and management. In addition, an unscheduled PK sample will be collected.
  b. If based upon the assessment by the cardiologist, the investigator considers that there is an acute cardiovascular safety risk and that the patient should not continue with study medication, the patient needs to be discontinued immediately (discontinuation criteria described in Section 7.1.7).
  c. If based upon the assessment by the cardiologist, the investigator considers that there is not an acute cardiovascular safety risk; the patient can continue to receive study medication.

Figure 7-2 QT Monitoring Flow Chart (except for Day 1)



* Please refer to Section 7.1.5, study treatment must be discontinued under this circumstance.

7.2.3 Pharmacokinetics

Blood samples for LCI699 PK evaluation will be collected from all patients who receive at least one dose of study treatment. Pharmacokinetic (PK) blood sampling will be performed in each study period as indicated in the Visit Evaluation Schedule (Table 7-1 to Table 7-3).

Time points of blood sample collection for sparse PK and extensive PK analyses are outlined in Table 7-10 and Table 7-1, respectively. The following PK sampling will be performed:

- Sparse PK assessment in all other patients: trough (predose) and peak (1 – 2 h post-dose). (Table 7-10)

- Extensive PK assessment (subset of n~20 patients): trough (predose), 0.25 – 0.75 h, 1 – 2 h, and 3 – 4 h post-dose during dose titration phase; trough (predose) and peak (1 – 2 h post-dose) beyond titration phase. (Table 7-11)
- [(**China only**):
  - Extensive sampling: trough (predose), 0.5, 1, 1.5, 2, 4, 6, 8 and 12 h post-dose during dose titration phase if there is a dose escalation; (Table 7-12)
  - Sparse sampling: trough (predose) and peak (1.5 h post-dose) if there is no dose escalation. (Table 7-12)

If LCI administration was interrupted prior to a planned visit and no study treatment is administered on the day of the planned visit, blood draw for PK sampling will not be required.

All ECG procedures should be taken prior to and/or 30 minutes after any PK blood draws since sampling for PK impacts ECG measurements.

Complete dosing information, including the date and time of actual blood draw and time of the last study treatment dose prior to the sampling (24-h clock time), should be obtained on all sampling days and recorded on the PK CRF and/or Contract Research Organization (CRO) requisition form(s). Sampling problems will be noted in the relevant field in the CRF.

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

Plasma samples remaining after completion of the determination of LCI699 may be used for exploratory analysis to further characterize the PK of LCI699 and its metabolite(s), such as metabolite profiling, and results will be reported separately.

7.2.3.1 Pharmacokinetic blood collection and handling

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

Blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. At specified time points described in Table 7-10 or Table 7-11, blood will be collected into tubes containing K2-EDTA and gently inverted several times to thoroughly mix the anticoagulant. Tubes will be centrifuged to separate plasma and plasma will immediately be transferred into labeled screw-cap polypropylene, cryogenic, freezing vials (e.g. Sarstedt, part# 72.693, no skirt). Plasma samples will be placed in a freezer in an upright position until shipment on dry ice to the Novartis assigned laboratory for analysis.

Table 7-10 Pharmacokinetic blood collection for sparse PK assessment

Visit	Week	Day	Scheduled time point [a]	PK collection number for dose after trough sample [b]	PK collection number prior to trough sample [b]	PK Sample No	Sample volume [mL]
3	0	1	Pre-dose/ 0 h	1		50	2.6
3	0	1	Post-dose 1 - 2 h	1		51	2.6
4	2	15	Pre-dose/ 0 h	2	102	52	2.6
4	2	15	Post-dose 1 - 2 h	2		53	2.6
5	4	29	Pre-dose/ 0 h	3	103	54	2.6
5	4	29	Post-dose 1 - 2 h	3		55	2.6
6	6	43	Pre-dose/ 0 h	4	104	56	2.6
6	6	43	Post-dose 1 - 2 h	4		57	2.6
7	8	57	Pre-dose/ 0 h	5	105	58	2.6
7	8	57	Post-dose 1 - 2 h	5		59	2.6
8	10	71	Pre-dose/ 0 h	6	106	60	2.6
8	10	71	Post-dose 1 - 2 h	6		61	2.6
9	12	85	Pre-dose / 0 h	7	107	62	2.6
9	12	85	Post-dose 1 - 2 h	7		63	2.6
10	16	113	Pre-dose / 0 h	8	108	64	2.6
10	16	113	Post-dose 1 - 2 h	8		65	2.6
11	20	141	Pre-dose / 0 h	9	109	66	2.6
11	20	141	Post-dose 1 - 2 h	9		67	2.6
12	24	169	Pre-dose / 0 h	10	110	68	2.6
12	24	169	Post-dose 1 - 2 h	10		69	2.6
13	26	183	Pre-dose / 0 h	11	111	70	2.6
14	28	197	Pre-dose / 0 h	12	112	71	2.6
15	30	211	Pre-dose / 0 h	13	113	72	2.6
16	32	225	Pre-dose / 0 h	14	114	73	2.6
17	34	239	Pre-dose / 0 h	15	115	74	2.6
18	36	253	Pre-dose / 0 h	16	116	75	2.6
19	40	281	Pre-dose / 0 h	17	117	76	2.6
20	44	309	Pre-dose / 0 h	18	118	77	2.6
777	48	337	Pre-dose / 0 h	---	119	78	2.6
Unscheduled Sample			---	---	---	2001+	2.6

[a] The following PK assessment windows are acceptable: pre-dose sample within 0.5 h before dose administration

[b] For the PK pre-dose (trough) samples, the actual date and time of administration of the previous dose of study medication should also be recorded with appropriate PK collection number as indicated in the above table. The PK collection number series “1, 2, 3…” is for the LCI699 dose administered on study visit day, while PK collection number series “102, 103, 104…” is for last LCI699 dose the patient received prior to the collection of the PK pre-dose (trough) sample

Table 7-11 Pharmacokinetic blood collection for extensive PK assessment (subset of approximately 20 patients)

Visit	Week	Day	Scheduled time point [a]	PK collection number for dose after trough sample [b]	PK collection number prior to trough sample [b]	PK Sample No	Sample volume [mL]
3	0	1	Pre-dose/ 0 h	201		1	2.6
3	0	1	Post-dose 0.25 - 0.75 h	201		2	2.6
3	0	1	Post-dose 1 - 2 h	201		3	2.6
3	0	1	Post-dose 3 - 4 h	201		4	2.6
4	2	15	Pre-dose/ 0 h	202	302	5	2.6
4	2	15	Post-dose 0.25 - 0.75 h	202		6	2.6
4	2	15	Post-dose 1 - 2 h	202		7	2.6
4	2	15	Post-dose 3 - 4 h	202		8	2.6
5	4	29	Pre-dose/ 0 h	203	303	9	2.6
5	4	29	Post-dose 0.25 – 0.75 h [c]	203		10	2.6
5	4	29	Post-dose 1 - 2 h	203		11	2.6
5	4	29	Post-dose 3 - 4 h [c]	203		12	2.6
6	6	43	Pre-dose/ 0 h	204	304	13	2.6
6	6	43	Post-dose 0.25 – 0.75 h [c]	204		14	2.6
6	6	43	Post-dose 1 - 2 h	204		15	2.6
6	6	43	Post-dose 3 - 4 h [c]	204		16	2.6
7	8	57	Pre-dose/ 0 h	205	305	17	2.6
7	8	57	Post-dose 0.25 – 0.75 h [c]	205		18	2.6
7	8	57	Post-dose 1 - 2 h	205		19	2.6
7	8	57	Post-dose 3 - 4 h [c]	205		20	2.6
8	10	71	Pre-dose/ 0 h	206	306	21	2.6
8	10	71	Post-dose 0.25 – 0.75 h [c]	206		22	2.6
8	10	71	Post-dose 1 - 2 h	206		23	2.6
8	10	71	Post-dose 3 - 4 h [c]	206		24	2.6
9	12	85	Pre-dose / 0 h	207	307	25	2.6
9	12	85	Post-dose 0.25 – 0.75 h [c]	207		26	2.6
9	12	85	Post-dose 1 - 2 h	207		27	2.6
9	12	85	Post-dose 3 - 4 h [c]	207		28	2.6
10	16	113	Pre-dose / 0 h	208	308	29	2.6
10	16	113	Post-dose 1 - 2 h	208		30	2.6
11	20	141	Pre-dose / 0 h	209	309	31	2.6
11	20	141	Post-dose 1 - 2 h	209		32	2.6
12	24	169	Pre-dose / 0 h	210	310	33	2.6
12	24	169	Post-dose 1 - 2 h	210		34	2.6
13	26	183	Pre-dose / 0 h	211	311	35	2.6
14	28	197	Pre-dose / 0 h	212	312	36	2.6
15	30	211	Pre-dose / 0 h	213	313	37	2.6
16	32	225	Pre-dose / 0 h	214	314	38	2.6
17	34	239	Pre-dose / 0 h	215	315	39	2.6
18	36	253	Pre-dose / 0 h	216	316	40	2.6
19	40	281	Pre-dose / 0 h	217	317	41	2.6

Visit	Week	Day	Scheduled time point [a]	PK collection number for dose after trough sample [b]	PK collection number prior to trough sample [b]	PK Sample No	Sample volume [mL]
20	44	309	Pre-dose / 0 h	218	318	42	2.6
777	48	337	Pre-dose / 0 h	---	319	43	2.6
Unscheduled Sample			---	---	---	1001+	2.6

[a] The following PK assessment windows are acceptable: pre-dose sample within 0.5 h before dose administration.

[b] For the PK pre-dose (trough) samples, the actual date and time of administration of the previous dose of study medication should also be recorded with appropriate PK collection number as indicated in the above table. The PK collection number series "201, 202, 203…" is for the LCI699 dose administered on study visit day, while PK collection number series "302, 303, 304…" is for last LCI699 dose the patient received prior to the collection of the PK pre-dose (trough) sample

[c] Required if dose is titrated since last visit. If the LCI699 dose was maintained (i.e. no dose titration since last visit), then only pre-dose and 1- 2 h samples are required.

[(**China only**) For profiles with extensive sampling, the pharmacokinetic parameters (Table 7-12) of LCI699 will be calculated from individual plasma concentration versus time profiles using non-compartmental analysis (Phoenix WinNonlin v. 6.2). PK parameter derivation will be based on actual time points (elapsed time).

If the LCI699 dose is maintained (i.e. no dose titration since last visit), only pre-dose and 1.5 h samples are required from Visit 5 to Visit 9.]

Table 7-12 [(China only) Pharmacokinetic blood collection for Chinese patients]

Visit	Week	Day	Scheduled time point [a]	PK collection number for dose after trough sample [b]	PK collection number prior to trough sample [b]	PK Sample No	Sample volume [mL]
3	0	1	Pre-dose/ 0 h	401		601	2.6
3	0	1	Post-dose 0.5 h	401		602	2.6
3	0	1	Post-dose 1 h	401		603	2.6
3	0	1	Post-dose 1.5 h	401		604	2.6
3	0	1	Post-dose 2 h	401		605	2.6
3	0	1	Post-dose 4 h	401		606	2.6
3	0	1	Post-dose 6 h	401		607	2.6
3	0	1	Post-dose 8 h	401		608	2.6
3	0	1	Post-dose 12 h	401		609	2.6
4	2	15	Pre-dose/ 0 h	402	502	610	2.6
4	2	15	Post-dose 0.5 h	402		611	2.6
4	2	15	Post-dose 1 h	402		612	2.6
4	2	15	Post-dose 1.5 h	402		613	2.6
4	2	15	Post-dose 2 h	402		614	2.6
4	2	15	Post-dose 4 h	402		615	2.6
4	2	15	Post-dose 6 h	402		616	2.6
4	2	15	Post-dose 8 h	402		617	2.6
4	2	15	Post-dose 12 h	402		618	2.6
If dose is maintained (i.e. no change from visit 4), only take pre-dose and 1.5 h samples							
5	4	29	**Pre-dose/ 0 h**	403	503	619	2.6
5	4	29	Post-dose 0.5 h [c]	403		620	2.6
5	4	29	Post-dose 1 h [c]	403		621	2.6
5	4	29	**Post-dose 1.5 h**	403		622	2.6
5	4	29	Post-dose 2 h [c]	403		623	2.6
5	4	29	Post-dose 4 h [c]	403		624	2.6
5	4	29	Post-dose 6 h [c]	403		625	2.6
5	4	29	Post-dose 8 h [c]	403		626	2.6
5	4	29	Post-dose 12 h [c]	403		627	2.6
If dose is maintained (i.e. no change from visit 5), only take pre-dose and 1.5 h samples							
6	6	43	**Pre-dose/ 0 h**	404	504	628	2.6
6	6	43	Post-dose 0.5 h [c]	404		629	2.6
6	6	43	Post-dose 1 h [c]	404		630	2.6
6	6	43	**Post-dose 1.5 h**	404		631	2.6
6	6	43	Post-dose 2 h [c]	404		632	2.6
6	6	43	Post-dose 4 h [c]	404		633	2.6
6	6	43	Post-dose 6 h [c]	404		634	2.6
6	6	43	Post-dose 8 h [c]	404		635	2.6
6	6	43	Post-dose 12 h [c]	404		636	2.6

Visit	Week	Day	Scheduled time point [a]	PK collection number for dose after trough sample [b]	PK collection number prior to trough sample [b]	PK Sample No	Sample volume [mL]
If dose is maintained (i.e. no change from visit 6), only take pre-dose and 1.5 h samples							
7	8	57	**Pre-dose/ 0 h**	405	505	637	2.6
7	8	57	Post-dose 0.5 h [c]	405		638	2.6
7	8	57	Post-dose 1 h [c]	405		639	2.6
7	8	57	**Post-dose 1.5 h**	405		640	2.6
7	8	57	Post-dose 2 h [c]	405		641	2.6
7	8	57	Post-dose 4 h [c]	405		642	2.6
7	8	57	Post-dose 6 h [c]	405		643	2.6
7	8	57	Post-dose 8 h [c]	405		644	2.6
7	8	57	Post-dose 12 h [c]	405		645	2.6
If dose is maintained (i.e. no change from visit 7), only take pre-dose and 1.5 h samples							
8	10	71	**Pre-dose/ 0 h**	406	506	646	2.6
8	10	71	Post-dose 0.5 h [c]	406		647	2.6
8	10	71	Post-dose 1 h [c]	406		648	2.6
8	10	71	**Post-dose 1.5 h**	406		649	2.6
8	10	71	Post-dose 2 h [c]	406		650	2.6
8	10	71	Post-dose 4 h [c]	406		651	2.6
8	10	71	Post-dose 6 h [c]	406		652	2.6
8	10	71	Post-dose 8 h [c]	406		653	2.6
8	10	71	Post-dose 12 h [c]	406		654	2.6
If dose is maintained (i.e. no change from visit 8), only take pre-dose and 1.5 h samples							
9	12	85	**Pre-dose/ 0 h**	407	507	655	2.6
9	12	85	Post-dose 0.5 h [c]	407		656	2.6
9	12	85	Post-dose 1 h [c]	407		657	2.6
9	12	85	**Post-dose 1.5 h**	407		658	2.6
9	12	85	Post-dose 2 h [c]	407		659	2.6
9	12	85	Post-dose 4 h [c]	407		660	2.6
9	12	85	Post-dose 6 h [c]	407		661	2.6
9	12	85	Post-dose 8 h [c]	407		662	2.6
9	12	85	Post-dose 12 h [c]	407		663	2.6
10	16	113	Pre-dose / 0 h	408	508	664	2.6
10	16	113	Post-dose 1.5 h	408		665	2.6
11	20	141	Pre-dose / 0 h	409	509	666	2.6
11	20	141	Post-dose 1.5 h	409		667	2.6
12	24	169	Pre-dose / 0 h	410	510	668	2.6
12	24	169	Post-dose 1 - 2 h	410		669	2.6
13	26	183	Pre-dose / 0 h	411	511	670	2.6
14	28	197	Pre-dose / 0 h	412	512	671	2.6
15	30	211	Pre-dose / 0 h	413	513	672	2.6
16	32	225	Pre-dose / 0 h	414	514	673	2.6
17	34	239	Pre-dose / 0 h	415	515	674	2.6
18	36	253	Pre-dose / 0 h	416	516	675	2.6
19	40	281	Pre-dose / 0 h	417	517	676	2.6
20	44	309	Pre-dose / 0 h	418	518	677	2.6

Visit	Week	Day	Scheduled time point [a]	PK collection number for dose after trough sample [b]	PK collection number prior to trough sample [b]	PK Sample No	Sample volume [mL]
777	48	337	Pre-dose / 0 h	---	519	678	2.6
Unscheduled Sample			---	---	---	3001+	2.6

[a] The following PK assessment windows are acceptable: pre-dose sample within 0.5 h before dose administration, ±10 min for up to the 2 h time points; ± 30 min for time points beyond 2 h.

[b] For the PK pre-dose (trough) samples, the actual date and time of administration of the previous dose of study medication should also be recorded with appropriate PK collection number as indicated in the above table. The PK collection number series "401, 402, 403…" is for the LCI699 dose administered on study visit day, while PK collection number series "502, 503, 504…" is for last LCI699 dose the patient received prior to the collection of the PK pre-dose (trough) sample

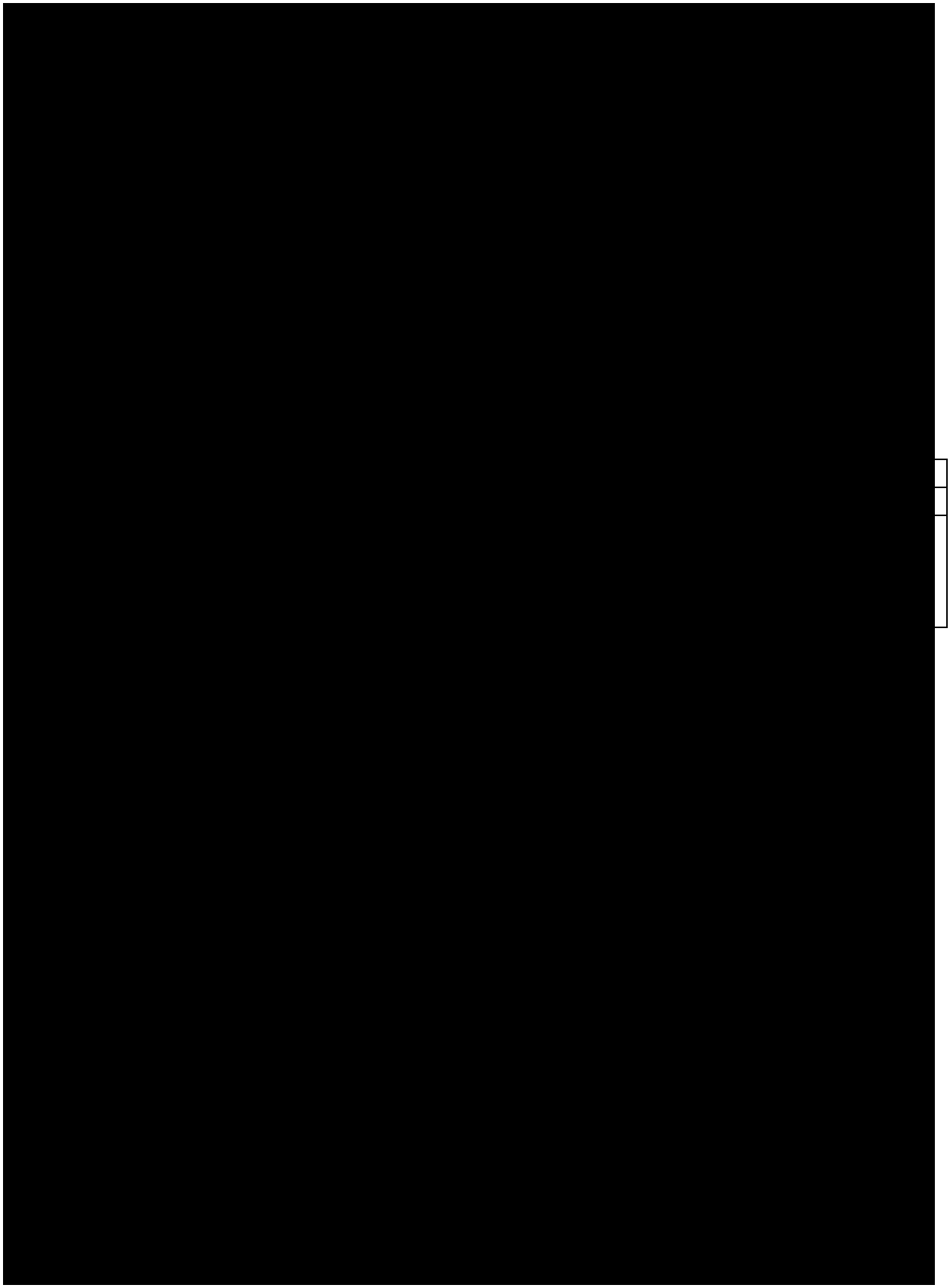
[c] Required if dose is titrated since last visit. If the LCI699 dose was maintained (i.e. no dose titration since last visit), **then only pre-dose and 1.5 h samples are required**.

Table 7-13 [(China only) Non-compartmental pharmacokinetic parameters]

AUClast	The area under the concentration-time curve from time zero to the last measurable concentration [ng*h/mL]
AUCinf	The area under the plasma concentration-time curve from time zero extrapolated to infinity when feasible [ng*h/mL]
Cmax	The maximum (peak) plasma concentration after single dose administration [ng/mL]
Tmax	The time to reach maximum plasma concentration following drug administration [h]
T1/2	The elimination half-life [h]
Cl/F	Apparent systemic clearance of drug from plasma [L/h]
Vz/F	Apparent volume of distribution during terminal phase [L]

7.2.3.2 Analytical method

The plasma samples from all patients will be assayed for LCI699 concentrations using a validated liquid chromatography - tandem mass spectrometry assay (LC-MS/MS). The lower limit of quantitation (LLOQ) will be 0.10 ng/mL for LCI699; values below LLOQ will be reported as zero ng/mL, and missing samples will be labeled accordingly. Concentrations of LCI699 will be expressed in mass per volume units (ng/mL). Placebo samples will be analyzed. A further refinement of this bioanalytical method may be conducted during the course of the study.



7.2.5 Resource utilization

Not applicable.

7.2.6 Patient reported outcomes

Three patient reported outcome instruments will be used to assess the impact of treatment on patient quality of life and symptom burden (see Appendix 4). Patients must be asked to complete each questionnaire prior to clinical assessments being undertaken, and these must be completed in accordance with the schedules listed in Table 7-1 to Table 7-3 and Table 7-16. Patient's refusal to complete all or any part of a questionnaire should be documented in the study data capture system and should not be captured as a protocol deviation. Patient questionnaires should be completed in the language most familiar to the patient. The patient should be given sufficient space and time to complete the questionnaire. The site personnel should check the questionnaire for completeness and ask the patient to complete any missing responses. The original questionnaire will be kept with the patient's file as the source document.

Completed questionnaire(s) and any unsolicited comments written by the patient should be reviewed and assessed by the investigator for responses which may indicate potential AEs or SAEs before any clinical study examinations. This assessment should be documented in study source records. If AEs or SAEs are confirmed, study investigators should not encourage the patient to change responses reported in the completed questionnaires. Study investigators must follow reporting instructions outlined in Section 8 (e.g. reference "Adverse Events" section) of the study protocol.

Table 7-16 Patient reported outcomes (PROs) collection plan

Patient Questionnaires[1]	Week	Day	Time
CushingQoL Beck Depression Inventory-II EQ-5D-5L	Mandated, week -1	Day -7 to -1	Prior to any clinical assessments or diagnostic testing.
CushingQoL Beck Depression Inventory-II EQ-5D-5L	Mandated, Week 4, 8, 12, 24, 26,28, 30,32 34, 48 (see Section 7.1)	Day 29, 57, 85, 169, 183, 197, 211, 225, 239, 337	Prior to any clinical assessments, drug dosing or diagnostic testing.
CushingQoL Beck Depression Inventory-II EQ-5D-5L	Optional Extension: Mandated, Week 72, 96, EOT extension	Day 505, 673, EOT extension	Prior to any clinical assessments, drug dosing or diagnostic testing.
[1] Patient Questionnaires should be completed in the sequence from most specific to most general: Cushing QoL → Beck Depression Inventory-II → EQ-FD-5L			

CushingQoL

The Cushing's Disease Health-Related Quality of Life Questionnaire (CushingQoL) (version 1.0) that was developed to evaluate quality of life in patients with Cushing's syndrome (Webb et al 2008). The CushingQoL is comprised of 12 items that capture patient responses on seven concepts: daily activities, healing and pain, mood and self-confidence, social concerns, physical appearance, memory and concern about the future. Content reliability, sensitivity to change and psychometric properties have been validated in patients with Cushing's disease (Nelson et al 2013).

For this study, the CushingQoL has been modified from the standard four-week recall to a one-week recall in order to be more sensitive to the changes in patient quality of life, specifically during the randomized withdrawal period, where it is believed that changes in Cushing's disease symptoms will occur rapidly once patients stop treatment.

BDI-II

The Beck Depression Inventory II (BDI-II) is a patient reported instrument that consists of 21 items designed to assess the intensity of depression in clinical and normal patients in the preceding two weeks. Each item is a list of four statements arranged in increasing severity about a particular symptom of depression.

EQ-5D-5L

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

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

Instructions to respondents are included in the questionnaire. The EQ-5D-5L measures 5 items on mobility, self-care, usual activities, pain/discomfort, anxiety/depression, measured on 5

levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ-5D-5L also includes a 20 cm vertical, VAS (visual analogue scale) with on a scale of 0-100, with endpoints labeled 'the best health you can imagine' and 'the worst health you can imagine'. A single index value is analyzed for the EQ-5D-5L and VAS score.

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Except for screening failures, adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Relevant Medical History/Current Medical Conditions CRF page of the patient's CRF. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected through a End Of Treatment / Study Evaluation completion CRF.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-4)
2. Its duration (Start and end dates, or Ongoing at End of Study)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given

6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

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

8.1.3 Adverse events of special interest

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest are defined on the basis of an ongoing review of the safety data. AESI are discussed in detail in the Investigator Brochure.

In addition to the AEs listed earlier (Section 1.2.1.2.2 and Section 1.2.1.2.3), other AEs are predicted by the underlying disease or the mechanism of action (MoA) of LCI699, specifically in patients with Cushing's disease. Many, but not all, of these AEs have been observed in preclinical and/or clinical studies.

These "AEs of Special Interest" includes the following mechanistic groups:

- Adrenal Hormone Precursor Accumulation-related AEs
- Hypocortisolism related AEs
- Pituitary tumor enlargement-related AEs

- QT-prolongation-related AEs
- Arrythmogenic potential AEs

Two of the AEs of special interest, the potential for QT prolongation and glucocorticoid withdrawal/hypocortisolism/adrenal insufficiency are described in greater detail below.

8.1.3.1 Risk of QT prolongation

Preclinical cardiac safety studies have revealed a signal of QT prolongation with LCI699 that is consistent across *in vitro* and *in vivo* studies. The risk was quantified in an ICH E-14 compliant thorough QT/QTc study conducted in healthy volunteers (see Section 1.2.1.2.4 for a summary of the results). The results support the use of LCI699 in doses up to 30 mg [LCI699C2105].

8.1.3.2 Glucocorticoid withdrawal/hypocortisolism/adrenal insufficiency

Important and closely related AEs of special interest are glucocorticoid withdrawal, hypocortisolism, and adrenal insufficiency. These AEs are a consequence of the potent activity of LCI699 to inhibit cortisol synthesis. In patients Cushing's disease, the relatively rapid correction of hypercortisolism can result in symptoms of glucocorticoid withdrawal. If the inhibition of cortisol synthesis is excessive, hypocortisolism or adrenal insufficiency may develop.

The patient should be questioned on the signs and symptoms of glucocorticoid withdrawal/hypocortisolism/adrenal insufficiency during all phone communications and during visits at the site. If any potential signs or symptoms are reported, they should be graded for severity and reported as an AE.

8.1.3.3 Definitions and reporting

Groupings of adverse event of special interest will be considered and the number of patients with at least one event in each grouping will be reported. Such groups consist of AEs for which there is a specific interest in connection with LCI699 treatment (i.e. where LCI699 may influence a common mechanism of action responsible for triggering them) or adverse event that are very similar although not identical. The groups will be defined according to criteria described in MedDRA.

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,

- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition

8.2.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided main informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the oncology Novartis Drug Safety and Epidemiology (DS&E) department.

The telephone and telefax number of the contact persons in the local department of Drug Safety and Epidemiology (DS&E), specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site. Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the [Investigator's Brochure] and is thought to be related to the Novartis study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and

reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Emergency unblinding of treatment assignment

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

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IRT.

Unblinding would only be considered if the emergency occurs during the randomized withdrawal period.

Study treatment must be interrupted once emergency unblinding has occurred.

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

8.4 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology Department (DS&E). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

8.5 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided [Investigator Brochure]. Additional safety information collected between IB updates will be communicated

in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.6 Data Monitoring Committee

Not applicable.

8.7 Steering Committee

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

It is expected that the SC will consist of eight members, seven of whom are experts in the treatment and investigation of patients with Cushing's disease and one cardiologist with expertise in drug-related QT prolongation. The membership will represent the following countries and/or regions: the US, Europe, and Asia.

Since nearly all the safety data in this trial is from open-label treatment with LCI699 (except for the 8-week randomized withdrawal period), it is not necessary to have a separate Data Monitoring Committee.

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

9 Data collection and management

9.1 Data confidentiality

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

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

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

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant

information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on CRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

The designated investigator staff will enter the data required by the protocol into the Case Report Forms. The CRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the CRFs and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered in the CRF is complete, accurate, and that entry and updates are performed in a timely manner.

Pharmacokinetic (PK) [redacted] (blood) samples drawn during the course of the study will be collected from the investigator sites and analyzed by Novartis or a central laboratory contracted by Novartis. The site staff designated by the investigator will enter the information required by the protocol onto the PK [redacted] Sample Collection CRFs, as well as onto the designated CRO's requisition form. One copy of the requisition form will be sent to the CRO with the relevant information (including study number, patient ID, etc.) and one copy will be retained by the site.

IRT, ECG tracings and Imaging (MRI and DXA) will be transferred to central readers. Method for data collection will be described in respective manuals. A [Laboratory Manual] will also be available for Central laboratory.

9.4 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staffs are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples for hematology, biochemistry, coagulation, thyroid panel, serum pregnancy test and others assessments (Testosterone, estradiol, Plasma ACTH, cortisol, 11-deoxycortisol Plasma and serum aldosterone, [redacted], Plasma 11-Deoxycorticosterone, Fasting Insulin and plasma glucose, HbA1C, Serum Androstenedione, DHEAS, Estrone) will be performed by a Central Laboratory. Results of analysis tested centrally will be reconciled and sent electronically to Novartis (or a designated CRO). Unscheduled laboratory analysis performed locally will be collected directly in CRF by the sites.

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

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

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

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

10 Statistical methods and data analysis

The primary analysis will be performed based on cumulative data collected up to the date when all enrolled patients have either completed or prematurely withdrawn from the core phase of study. The results and outcomes of this analysis will be presented in a CSR. All additional data collected subsequently to the cutoff date for the primary analysis will be included in the analysis for the final CSR, which will be performed once all patients have either completed the extension

phase or discontinued earlier. Additional database lock/analysis could be performed after the primary analysis to support the publication of manuscripts.

Novartis or designated CRO will analyze all data using the Statistical Analysis System (SAS) for data analysis V9.3 or higher. Any data analyses carried out independently by an investigator should be submitted to Novartis before publication or presentation.

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

10.1 Analysis sets

10.1.1 Randomized Analysis Set

The Randomized Analysis Set (RAS) comprises all randomized patients who have received at least one dose of randomized drug (LCI699 or placebo). According to the ITT principle, patients will be analyzed according to the treatment and stratum they have been assigned to during the randomization.

10.1.2 Full Analysis Set

The Full Analysis Set (FAS) comprises all enrolled patients who receive at least one dose of LCI99. This is the default analysis set for efficacy.

10.1.3 Safety set

There are two safety sets defined in this study:

Safety Analysis Set (SAS) includes all patients who received at least one dose of LCI699 and had at least one valid post-baseline safety assessment.

Safety Analysis Set for randomized withdrawal period (SASR) includes only randomized patients who received at least one dose of randomized treatment (LCI699 or placebo) and had at least one valid safety assessment during the randomized withdrawal period.

Please note: the statement that a patient had no adverse events (on the Adverse Event CRF) constitutes a safety assessment.

For safety analysis, patients will be analyzed according to the study treatment received, where treatment received is defined as the randomized/assigned treatment if the patient took at least one dose of that treatment or the first treatment (first dose of the study for SAS and first dose of randomized withdrawal period for SASR) received if the randomized/assigned treatment was never received.

10.1.4 Per-Protocol set

There are two per-protocol sets defined in this study:

Per-Protocol Set for Randomized Analysis Set (PPRAS) consists of a subset of the patients in the RAS who are compliant with the requirements of the Clinical Study Protocol (CSP) and have no selected CSR-reportable protocol deviations.

Per-Protocol Set for Full Analysis Set (PPFAS) consists of a subset of the patients in the FAS who are compliant with the requirements of the CSP and have no selected CSR-reportable protocol deviations.

The details of selected CSR-reportable protocol deviations will be provided in the SAP.

10.1.5 Pharmacokinetic analysis set

The pharmacokinetic analysis set (PAS) consists of all patients who receive at least one dose of LCI699 and have at least one evaluable pharmacokinetic concentration (post-first-dose) at any visit.

Additional definition of an evaluable PK blood sample will be further specified in the SAP.

10.1.6 Other analysis sets

Not Applicable.

10.1.6.1 Efficacy/evaluable set

Not Applicable.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data will be summarized descriptively for the FAS and RAS.

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

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term, by treatment group using FAS and RAS.

10.3 Treatments (study treatment, concomitant therapies, compliance)

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

For patients in RAS/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

For patients in SAS

- LCI699 group: patients receiving continued treatment of LCI699 for the randomized withdrawal period of the study
- Placebo group: patients receiving placebo for the randomized withdrawal period of the study
- Non-randomized patients: patients who do not enter randomized withdrawal period of the study

For patients in SASR

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

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure (Week) to study drugs will be summarized by means of descriptive statistics.

The number of patients with dose reductions, interruption, or permanent discontinuation and the reasons will be listed and summarized by treatment arms, and all dosing data will be listed. Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, preferred term and treatment groups. The doses and dosing frequency of concomitant medications for the treatment of hypertension, diabetes, and dyslipidemia captured on the concomitant medication CRF, will be taken into account in the analysis of safety and efficacy.

10.4 Primary objective

The primary objective is 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.

10.4.1 Variable

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 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.

10.4.2 Statistical hypothesis, model, and method of analysis

For the primary objective, the statistical null hypothesis states that the complete response rates at the end of 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 ≤ 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.

10.4.3 Handling of missing values/censoring/discontinuations

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

Randomized patients who discontinued during the randomized withdrawal period or had a missing mUFC assessment at end of the randomized withdrawal period (Week 34) will be counted as non-responders for the primary endpoint.

10.4.4 Supportive and sensitivity analyses

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

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

10.5 Secondary objectives

10.5.1 Key secondary objective(s)

The key secondary objective is to assess the complete response rate (proportion of enrolled patients with mUFC $\leq$ ULN) 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 the end of 24 weeks open label period of LCI699 treatment is ≤ 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 ≥ 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 primary analysis of the key secondary endpoint will be performed using FAS. An additional analysis will be performed using PPFAS.

10.5.2 Other secondary efficacy objectives

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

Time-to-last control of mUFC during the randomized withdrawal period will be analyzed using K-M plot and stratified logrank test. Time-to-last control of mUFC is defined as the time (in days) from randomization to the time of the last normal UFC assessment (mUFC ≤ ULN based on central laboratory result) before early discontinuation or completion of randomized withdrawal period, whichever is earlier. RAS will be used for this analysis.

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

Proportion of complete responder (enrolled patients with mUFC ≤ ULN), partial responder (enrolled patients with mUFC > ULN and at least 50% reduction from baseline), and overall responder (enrolled patients with mUFC ≤ ULN or have at least 50% reduction from baseline) at Week 12 (end of period 1), Week 24 (end of period 2) and Week 48 (end of period 4) as well as at scheduled time points during the extension period (provided adequate follow-up as specified in the SAP) and the last available assessment will be summarized using point estimates and 95% CIs.

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

For the actual and percentage change in mUFC from baseline, descriptive summaries will be provided for every visit in core and extension (provided adequate follow-up as specified in the SAP) at which UFC is collected. 95% CIs for the percentage change from baseline will also be provided.

For the actual and percentage change in mUFC from the randomization (Week 26) to the end of randomized withdrawal period, or the last mUFC measurement prior to early discontinuation, whichever occurs earlier, in addition to the descriptive summaries, the difference between two randomized arm and associated 95% C.I. will be estimated with adjustment for mUFC at randomization. RAS will be used for the analysis.

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

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

For actual and percentage change from baseline during the core and extension period (provided adequate follow-up as specified in the SAP) of the study, descriptive summaries will be provided.

For the actual and percentage change from the randomization (Week 26) to the end of randomized withdrawal period, or the last measurement available prior to early discontinuation, whichever occurs earlier, in addition to the descriptive summary, the difference between two randomized arm and associated 95% C.I. will be estimated with adjustment for corresponding parameter value at randomization. RAS will be used for the analysis.

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

For each of physical features of Cushing's disease: facial rubor, hirsutism, striae, supraclavicular fat pad, dorsal fat pad, proximal muscle wasting (atrophy), central (abdominal) obesity, and ecchymoses (bruises). The change from baseline at Week 12, 24, 34 and 48 as well as during the extension at Week 72 and EOT extension will be assessed using shift table.

10.5.2.6 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.

10.5.2.7 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 mUFC has occurred (mUFC≤ULN)
- both the mean UFC 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).

For patients who attained normal mUFC (≤ ULN), time-to-escape will be analyzed using K-M plot. 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 discontinuation of LCI699 treatment (censored), whichever occurs earlier.

Patients randomized to placebo are not included in this analysis.

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

Analysis set and treatment groups (see Section 10.1 and Section 10.3) used for safety analyses will be described below:

- For study period up to Week 26: SAS by All patients only.
- For randomized withdrawal period: SASR by LCI699 group and Placebo group
- For overall study period while on LCI699: SAS by LCI699 group, Placebo group, Non-randomized patients, and all patients.
- In addition to the above mentioned analysis, other post-treatment safety data collected will be included in listings and flagged as appropriate.

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

1. pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
2. on treatment period: from day of first dose of study medication to 30 days after last dose of study medication
3. post-treatment period: starting at day 31 after last dose of study medication

10.5.3.2 Adverse events (AEs)

Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period, the **treatment-emergent** AEs. However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged. The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE version 4.03 grades), type of adverse event, relation to study treatment.

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

All deaths will be listed.

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

10.5.3.3 Laboratory abnormalities

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

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

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

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

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

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

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each patient will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE v4.03 grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE v4.03, shift tables based on the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value. In addition to the above mentioned tables and listings, other exploratory analyses, for example figures plotting time course of raw or change in laboratory tests over time or box plots might be specified in the SAP.

10.5.3.4 Other safety data

ECG

ECG data will be summarized with

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

Vital signs

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

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

Tumor volume

For tumor volume evaluated by MRI (or CT) scanning, descriptive summary of actual tumor volumes as well as its actual and percent change from baseline will be provided. The number and percentage of patients with newly occurring measurable tumor and/or new evidence of tumor invasion into surrounding structures during the study will be calculated. For MRI (or CT) images that are not interpretable for tumor volume, the longest dimension (in mm) will be summarized instead.

10.5.3.5 Supportive analyses for secondary objectives

Not applicable.

10.5.3.6 Tolerability

Tolerability will be studied in terms of dose reductions or drug interruption due to an AE.

10.5.4 Pharmacokinetics

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

As sparse pharmacokinetic sampling is performed in this study, traditional non-compartmental analysis will not be performed to calculate pharmacokinetic parameters. Plasma concentration data of LCI699 will be listed by patient, visit, incident dose and nominal sampling times. Descriptive statistics of plasma concentrations will be provided by incident dose, visit and nominal sampling times. Graphical depiction (mean and individual) for LCI699 concentrations and/or profiles (if applicable) during the course of the study will be performed by incident dose and visit. Additional details on PK data analysis will be specified in the SAP.

PK data generated from this study will be used in conjunction with PK data from other clinical studies in population PK assessment. Patient demographics (e.g. age, gender, ethnicity, weight) will be explored as covariates, if appropriate. The broad principles outlined in the FDA "Guidance for Industry: Population Pharmacokinetics" will be followed during the population PK analysis. The results of population PK assessment will be presented in a separate report.

[(China only) Plasma concentration data of LCI699 will be listed by patient, visit, incident dose and nominal sampling times. Descriptive statistics of plasma concentrations will be provided by incident dose, visit and nominal sampling times. For the extensive sampling profiles, graphical depiction (mean and individual) for LCI699 concentrations and/or profiles (if applicable) during the course of the study will be performed by incident dose and visit. Descriptive statistics will be reported for all PK parameters (including AUClast, AUCinf, Cmax, Tmax, T1/2, Cl/F, Vz/F) for LCI699 from the extensive sampling profiles. For sparse sampling data, traditional non-compartmental analysis will not be performed. PK data from this study will be used in conjunction with PK data from other clinical studies in population PK assessment.]

10.5.4.1 Data handling principles

Plasma concentrations of LCI699 will be expressed in ng/mL. Missing concentration values will be labeled as such in data listings. Concentrations below the limit of quantitation (LLOQ) will be treated as zero in summary statistics and reported as zero in data listings.

[redacted]

10.5.6 Resource utilization

Not Applicable.

10.5.7 Patient-reported outcomes

The CushingsQoL score is identified as the primary PRO variable of interest. EQ-5D utility index and visual analogue scale (VAS) scores, and Beck Depression Inventory-II (BDI) total score are identified as secondary PRO variables of interest. The FAS will be used for analyzing PRO data. No multiplicity adjustment will be applied.

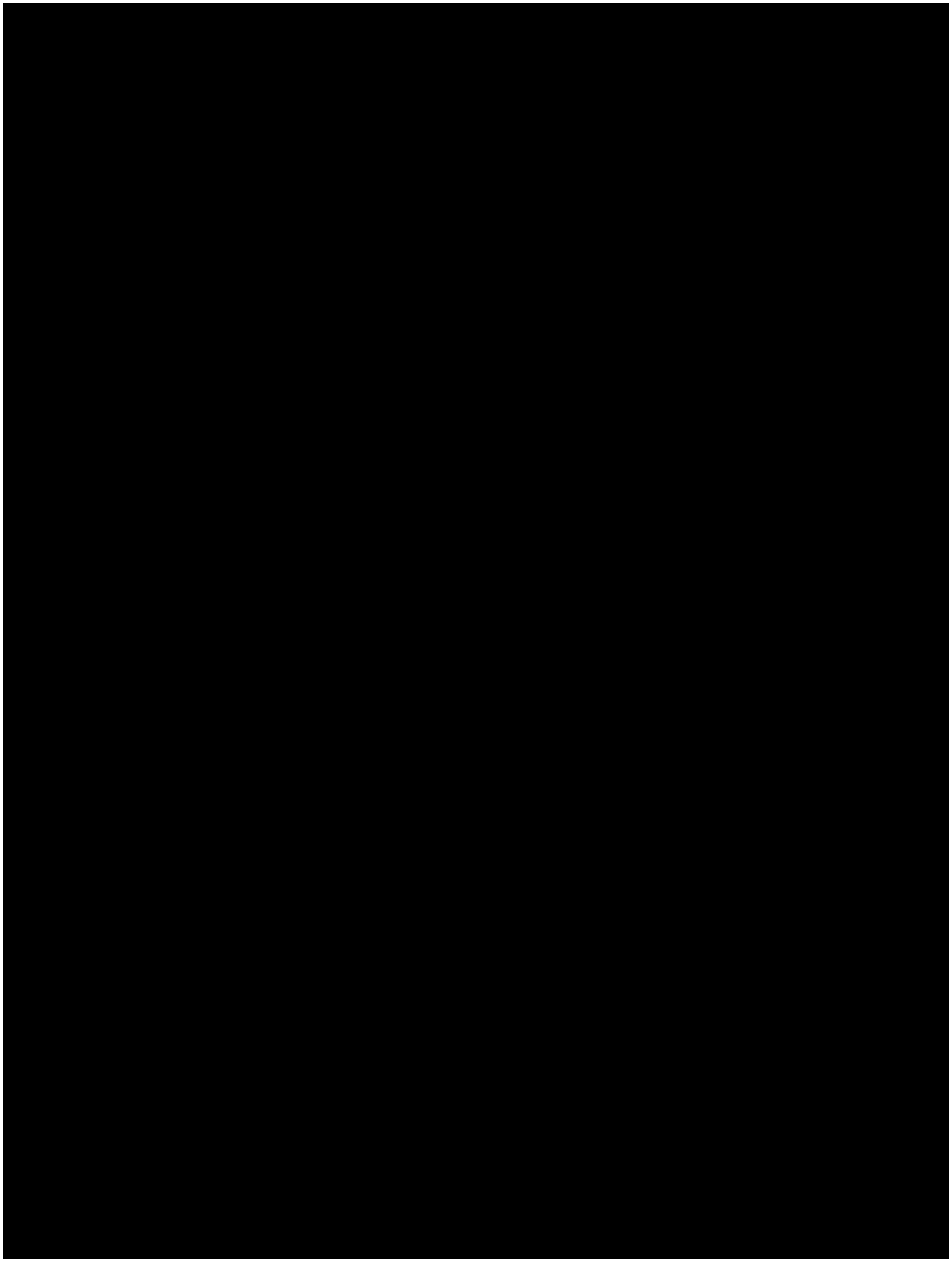
Change from Week 24 in the CushingsQoL score during Study Period 3 will be analyzed using a linear mixed effect model for longitudinal data to assess the treatment effect over time including terms for treatment, stratification factors, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by time of visit interaction, and Week 24 score. The differences in least square means between LCI699 and placebo group, and the corresponding 2-sided 95% confidence interval (CI) at each timepoint will be presented. Descriptive statistics will be used to summarize the raw and absolute change from baseline for the scores at each scheduled assessment during the core and extension periods (Week 72, 96, and EOT extension) of the study.

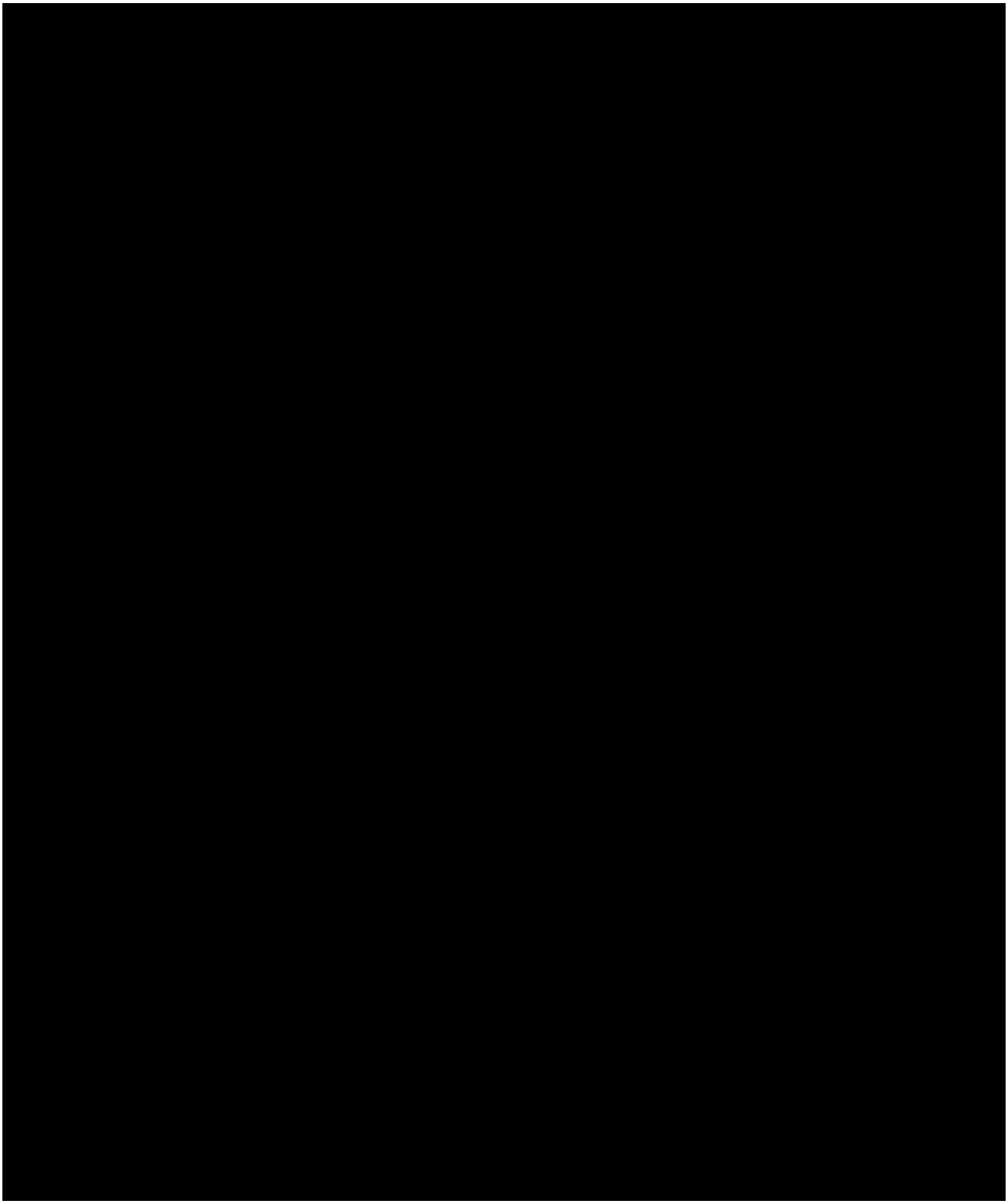
Similar analyses will be performed for EQ-5D utility index and visual analogue scale (VAS) scores, and Beck Depression Inventory-II (BDI) total score.

Missing items data in a scale will be handled based on each instrument manual. Additional details for handling missing items data will be specified in the analysis plan for instruments with no missing data handling criteria in the instrument manual.

No imputation will be applied if the total scores are missing at a visit. Patients with Week 26 and at least one non-missing post-Week 24 assessments during the Study Period 3 will be included in the linear mixed effect model analysis. All available data until completion or early discontinuation during Period 3 will be used in the linear mixed effect models analyses which assume that the missing scores at any time point are missing-at-random. Additional sensitivity analysis may be performed to assess the possible violation of missing-at-random assumption for the missing data mechanism if deemed appropriate. Details will be specified in the SAP.

[redacted]





10.7 Interim analysis

The study has no planned interim analysis for efficacy.

10.8 Sample size calculation

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:

1. 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.
2. 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.
3. 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.

10.9 Power for analysis of key secondary variables

The analysis of the key secondary objective will be based on the 2-sided 95% confidence interval constructed using the Clopper-Pearson exact method. If the lower bound of this 95% confidence interval is ≥ 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 C.I. of observed response rate (based on Clopper-Pearson Exact method) is larger than 30.0%.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their CRFs.

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

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

11.4 Discontinuation of the study

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

11.5 Publication of study protocol and results

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

11.5.1 Communication and publication of clinical trial results

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

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

Accordingly, ALL AUTHORS MUST HAVE:

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

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

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records,

clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Consult with DRA whether the study need to be covered by financial disclosures.

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study

to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

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14 Appendices

14.1 Appendix 1: Summary of Common Toxicity Criteria for Adverse Events v4.03 (CTCAE)

Table 14-1 List of summary of Common Toxicity Criteria for Adverse Events v4.03 (CTCAE)

Grade	Definition of Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
3	Severe or medically significant but not immediately life-threatening hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
4	Life-threatening consequences; urgent intervention indicated
5	Death related to AE

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

14.2 Appendix 2: List of drugs to be used with caution with LCI699

Table 14-2 List of medications with potential drug-drug interactions with LCI699 – to be used with caution

CYP1A2 substrates	CYP2C19 substrates	CYP2D6 substrates	CYP3A4/5 substrates	CYP2E1 substrates
Atypical antipsychotics: Clozapine Olanzapine **Xanthines:** Caffaine[1] Theophylline[2] **Others:** Nabumetone Riluzole Ropivacaine Zolmitriptan Alosetron[1] Duloxetine[1] Melatonin[1] Ramelteon[1] Tacrine[1] Tizanidine[1,2]	**Anti-epileptics:** Diazepam Phenytoin Phenobarbitone S-mephenytoin[1,2] **Benzodiazepines:** Clobazam[1] **Proton pump inhibitors:** Lansoprazole[1] Omeprazole[1] Pantoprazole Rabeprazole Esoprazole **Antidepressants:** Amitriptyline Clomipramine **Others:** Clopidogrel Moclobemide Proguanil	**Antipsychotics:** Aripiprazole Chlorpromazine Clozapine Fluphenazine Haloperidol Iloperidone Pimozide Risperidone Perphenazine[1] Thioridazine[2] **Antiarrhythmics:** Encainide Flecaninide Mexilletine Prajmaline Procainamide Propafenone Sparteine Vernakalant **Alpha/Beta-adrenergic antagonists:** Metoprolol[1] Nebivolol[1] Carvedilol Propranolol Tamsulosin Timolol **Serotonin modulators:** Venlafaxine[1] Citalopram Duloxetine Fluoxetine Fluvoxamine Nefazodone Ondansetron Paroxetine Repinotan Trazodone Tropisetron **Tricyclics/ tetracyclics:** Desipramine[1]	**Antiarrhythmics:** Quinidine[2] Dronedarone[1] **Antihistimines:** Astemizole[2] Ebastine[1] Terfenadine[1,2] **Benzodiazepines:** Brotizolam[1] Midazolam[1] Triazolam[1] Alprazolam Diazepam **Calcium channel blockers:** Felodipine[1] Nisoldipine[1] Amlodipine Diltiazem Nifedipine Nitrendipine Verapamil **Protease inhibitors:** Brecanavir[1] Capravirine[1] Darunavir[1] Indinavir[1] Lopinavir[1] Saquinavir[1] Tipranavir[1] Boceprevir Ritonavir Telaprevir **HMG CoA reductase inhibitors:** Atorvastatin[1] Lovastatin[1] Simvastatin[1] **Antibiotics:** Clarithromycin Erythromycin Telithromycin **Antipsychotics:** Aripiprazole Haloperidol	Enflurane Halothane Isoflurane Methoxyflurane Sevoflurane Acetaminophen Chlorzoxazone Ethanol N, N-Dimethylformamide Theophylline

		Amitriptyline Clomipramine Doxepin Imipramine Maprotiline Mianserin Mirtazapine Nortriptyline Trimipramine **Opiods:** Codeine Dihydrocodeine Hydrocodone Methadone Oxycodone Tramadol **Others:** Atomoxetine[1] Dextromethorphan[1] Tolterodine[1] Amiflamine Brofaromine Chlorpheniramine Debrisoquine Dexfenfluramine Donepezil Fesoterodine Gefitinib Lasofoxifene Loratadine Methamphetamine Methoxyphenamine Methylphenidate Nicergolin Pactimibe Phenformin Ranolazine Ratonavir Sabeluzole Tamoxifen Traxoprodil	Lurasidone[1] Perospirone[1] Pimozide[2] Quetiapine[1] **Immune Modulators:** Cyclosporine[2] Everolimus[1] Sirolimus[1,2] Tacrolimus[1,2] **Tyrosine Kinase Inhibitors:** Dasatinib[1] Neratinib[1] Imatinib Nilotinib **Opioids:** Alfentanil[1,2] Fentanyl[2] Levomethadyl[1] Methadone Others: Quinine Tamoxifen Trazodone Vincristine **Ergot derivatives:** Diergotamine/ Dihydroergotamin[2] Ergotamine[2] **Erectile dysfunction agents:** Sildenafil[1] Vardenafil[1] **Antiemetics:** Aprepitant[1] Casopitant[1] **Others:** Alpha-dihydroergocryptine[1] Aplaviroc[1] Buspirone[1] Cisapride[2] Conivaptan[1] Darifenacin[1] Eletriptan[1] Eplerenone[1] Lumefantrine[1] Maraviroc[1] Ridaforolimus[1] Ticagrelor[1] Tolvaptan[1]	

			Vicriviroc[1]	

[1] Sensitive substrates: drugs that exhibit an AUC ratio (AUCi/AUC) of 5-fold or more when co-administered with a known potent inhibitor.

[2] Substrates with narrow therapeutic index: drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns.

This database of CYP substrates was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table; from the FDA's "Guidance for Industry, Drug Interaction Studies" and from the University of Washington's Drug Interaction Database.

14.3 Appendix 3: Medications with a “Known risk to cause TdP” and with a “Possible risk to cause TdP”

The following e-link provides a list of medications with a “known risk to cause TdP” and with a “possible risk to cause TdP”. These medications are prohibited to be used concomitantly with LCI699: www.crediblemeds.org.

Investigators are advised to utilize this website when considering the addition of a new concomitant medication, as the lists are periodically updated. If necessary, a discussion can be held with the Novartis Medical Monitor when considering the use of medications with a “known risk to cause TdP” and with a “possible risk to cause TdP”.

14.4 Appendix 4: Patient Quality of Life questionnaires

EQ-5D-5L Questionnaire

Under each heading, please check the ONE box that best describes your health TODAY

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

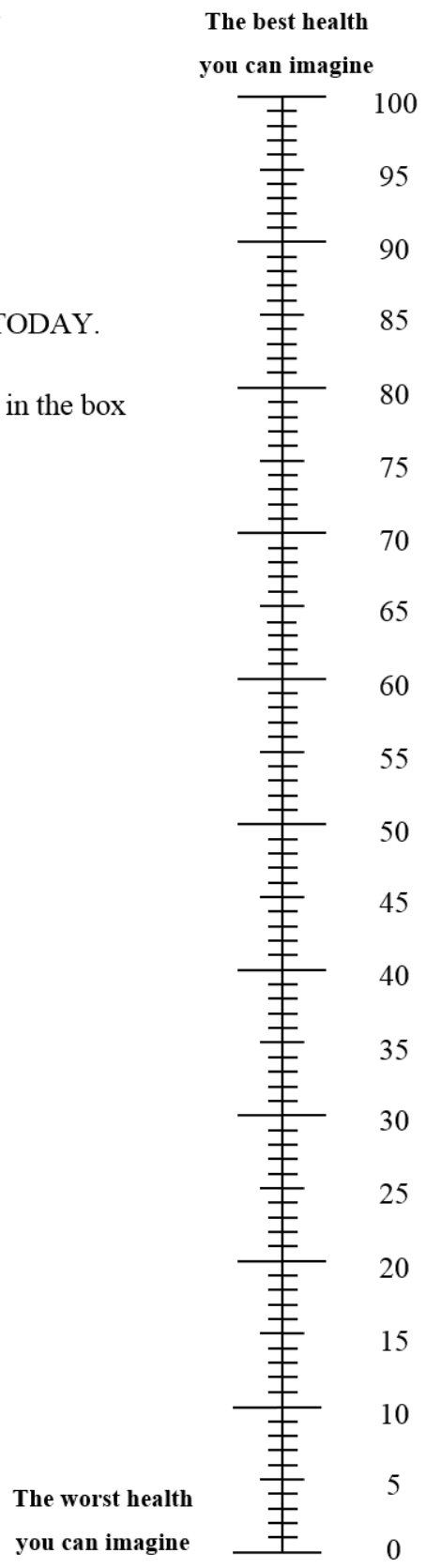
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Cushing's Syndrome Quality Of Life Questionnaire

The following sentences refer to what you may think or feel about your Cushing's syndrome. Your answers will help us to know how you feel and how much your illness has interfered in your usual activities in **the past 4 weeks**.

Below each sentence you will find several response choices. Please read each sentence carefully. After reading each sentence, check the box next to the answer that best describes what you think is happening to you.

There are NO right or wrong answers. We are simply interested in what is happening to you because of your Cushing's syndrome.

1. I have trouble sleeping (I wake up during the night; it takes me a long time to get to sleep, etc.).
   ☐ Always
   ☐ Often
   ☐ Sometimes
   ☐ Rarely
   ☐ Never

2. I have pain that keeps me from leading a normal life.
   ☐ Always
   ☐ Often
   ☐ Sometimes
   ☐ Rarely
   ☐ Never

3. My wounds take a long time to heal.
   ☐ Always
   ☐ Often
   ☐ Sometimes
   ☐ Rarely
   ☐ Never

4. I bruise easily.
   ☐ Always
   ☐ Often
   ☐ Sometimes
   ☐ Rarely
   ☐ Never

5. I am more irritable, I have sudden mood swings and angry outbursts.
   ☐ Always
   ☐ Often
   ☐ Sometimes
   ☐ Rarely
   ☐ Never

6. I have less self-confidence, I feel more insecure.
   ☐ Always
   ☐ Often
   ☐ Sometimes
   ☐ Rarely
   ☐ Never

7. I'm worried about the changes in my physical appearance due to my illness.
   ☐ Always
   ☐ Often
   ☐ Sometimes
   ☐ Rarely
   ☐ Never

8. I feel less like going out or seeing relatives or friends.
   ☐ Always
   ☐ Often
   ☐ Sometimes
   ☐ Rarely
   ☐ Never

9. I have had to give up my social or leisure activities due to my illness.
   ☐ Always
   ☐ Often
   ☐ Sometimes
   ☐ Rarely
   ☐ Never

10. My illness affects my everyday activities such as working or studying.
    ☐ Always
    ☐ Often
    ☐ Sometimes
    ☐ Rarely
    ☐ Never

11. It’s difficult for me to remember things.
    - ☐ Always
    - ☐ Often
    - ☐ Sometimes
    - ☐ Rarely
    - ☐ Never

12. I’m worried about my health in the future.
    - ☐ Always
    - ☐ Often
    - ☐ Sometimes
    - ☐ Rarely
    - ☐ Never

Beck Depression Inventory Questionnaire

This depression inventory can be self-scored. The scoring scale is at the end of the questionnaire.

1.
   0 I do not feel sad.
   1 I feel sad
   2 I am sad all the time and I can't snap out of it.
   3 I am so sad and unhappy that I can't stand it.
2.
   0 I am not particularly discouraged about the future.
   1 I feel discouraged about the future.
   2 I feel I have nothing to look forward to.
   3 I feel the future is hopeless and that things cannot improve.
3.
   0 I do not feel like a failure.
   1 I feel I have failed more than the average person.
   2 As I look back on my life, all I can see is a lot of failures.
   3 I feel I am a complete failure as a person.
4.
   0 I get as much satisfaction out of things as I used to.
   1 I don't enjoy things the way I used to.
   2 I don't get real satisfaction out of anything anymore.
   3 I am dissatisfied or bored with everything.
5.
   0 I don't feel particularly guilty
   1 I feel guilty a good part of the time.
   2 I feel quite guilty most of the time.
   3 I feel guilty all of the time.
6.
   0 I don't feel I am being punished.
   1 I feel I may be punished.
   2 I expect to be punished.
   3 I feel I am being punished.
7.
   0 I don't feel disappointed in myself.
   1 I am disappointed in myself.
   2 I am disgusted with myself.
   3 I hate myself.
8.
   0 I don't feel I am any worse than anybody else.
   1 I am critical of myself for my weaknesses or mistakes.
   2 I blame myself all the time for my faults.
   3 I blame myself for everything bad that happens.

9.
- 0 I don't have any thoughts of killing myself.
- 1 I have thoughts of killing myself, but I would not carry them out.
- 2 I would like to kill myself.
- 3 I would kill myself if I had the chance.

10.
- 0 I don't cry any more than usual.
- 1 I cry more now than I used to.
- 2 I cry all the time now.
- 3 I used to be able to cry, but now I can't cry even though I want to.

11.
- 0 I am no more irritated by things than I ever was.
- 1 I am slightly more irritated now than usual.
- 2 I am quite annoyed or irritated a good deal of the time.
- 3 I feel irritated all the time.

12.
- 0 I have not lost interest in other people.
- 1 I am less interested in other people than I used to be.
- 2 I have lost most of my interest in other people.
- 3 I have lost all of my interest in other people.

13.
- 0 I make decisions about as well as I ever could.
- 1 I put off making decisions more than I used to.
- 2 I have greater difficulty in making decisions more than I used to.
- 3 I can't make decisions at all anymore.

14.
- 0 I don't feel that I look any worse than I used to.
- 1 I am worried that I am looking old or unattractive.
- 2 I feel there are permanent changes in my appearance that make me look unattractive
- 3 I believe that I look ugly.

15.
- 0 I can work about as well as before.
- 1 It takes an extra effort to get started at doing something.
- 2 I have to push myself very hard to do anything.
- 3 I can't do any work at all.

16.
- 0 I can sleep as well as usual.
- 1 I don't sleep as well as I used to.
- 2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
- 3 I wake up several hours earlier than I used to and cannot get back to sleep.

17.
- 0 I don't get more tired than usual.
- 1 I get tired more easily than I used to.
- 2 I get tired from doing almost anything.
- 3 I am too tired to do anything.

18.
- 0 My appetite is no worse than usual.
- 1 My appetite is not as good as it used to be.
- 2 My appetite is much worse now.
- 3 I have no appetite at all anymore.

19.
- 0 I haven't lost much weight, if any, lately.
- 1 I have lost more than five pounds.
- 2 I have lost more than ten pounds.
- 3 I have lost more than fifteen pounds.

20.
- 0 I am no more worried about my health than usual.
- 1 I am worried about physical problems like aches, pains, upset stomach, or constipation.
- 2 I am very worried about physical problems and it's hard to think of much else.
- 3 I am so worried about my physical problems that I cannot think of anything else.

21.
- 0 I have not noticed any recent change in my interest in sex.
- 1 I am less interested in sex than I used to be.
- 2 I have almost no interest in sex.
- 3 I have lost interest in sex completely.

INTERPRETING THE BECK DEPRESSION INVENTORY

Now that you have completed the questionnaire, add up the score for each of the twenty-one questions by counting the number to the right of each question you marked. The highest possible total for the whole test would be sixty-three. This would mean you circled number three on all twenty-one questions. Since the lowest possible score for each question is zero, the lowest possible score for the test would be zero. This would mean you circles zero on each question.

You can evaluate your depression according to the Table below.

Total Score	Levels of Depression
1-10	These ups and downs are considered normal
11-16	Mild mood disturbance
17-20	Borderline clinical depression
21-30	Moderate depression
31-40	Severe depression
over 40	Extreme depression

A PERSISTENT SCORE OF 17 OR ABOVE INDICATES THAT YOU MAY NEED MEDICAL TREATMENT. IF YOU HAVE ANY CARDIAC CONCERNS, PLEASE CONTACT CARDIOVASCULAR INTERVENTIONS, P.A. at 407-894-4880