NOVARTIS

Translational Sciences/Oncology

LCI699 (osilodrostat)

Clinical Study Protocol CLCI699C2201 / NCT01331239

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

Authors:	[redacted]
Document type:	Amended Protocol Version
EUDRACT number:	2010-022403-22
Version number:	09 (Clean)
Development phase:	II
Release date:	03-May-2018

[redacted]

Table of contents

[redacted]

[redacted]

[redacted]

[redacted]

List of tables

List of figures

[redacted]

List of abbreviations

ACTH	Adrenocorticotropic Hormone
AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
b.i.d.	twice a day
CD	Cushing's disease
(e)CRF	(electronic) Case Report/Record Form
CNS	Central Nervous System
CPO	Country Pharma Organization
CRH	Corticotropin Releasing Hormone
CRO	Contract Research Organization
CS	Cushing's syndrome
CYP	Cytochrome P450
DILI	Drug-induced liver injury
CMO&PS	Chief Medical Office and Patient Safety
ECG	Electrocardiogram
EDC	Electronic Data Capture
FPG	Fasting Plasma Glucose
$HbA1_c$	Glycosylated Hemoglobin
HOMA	Homeostasis Model of Assessment
HPA(-Axis)	Hypothalamic Pituitary Adrenal
IC50	Half Maximal Inhibitory Concentration
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
i.v.	intravenous
IRB	Institutional Review Board
LDH	Lactate dehydrogenase
LFT	Liver function test
LLN	Lower limit of normal
MDRD	Modification of Diet in Renal Disease
MEN-1	Multiple Endocrine Neoplasia Type 1
MRI	Magnetic Resonance Imaging
NOAEL	No Observable Adverse Effect Level
p.o.	oral
q.d.	once a day
SAE	serious adverse event
TdP	Torsades de Pointes
TBIL	Total Bilirubin
UFC	Urinary Free Cortisol
ULN	Upper Limit of Normal

[redacted]

Pharmacokinetic definitions and symbols

AUC0-6hr,ss	AUC at steady state 0-6hr post dose (ng.hr/mL)
AUC0-12hr,ss	The AUC from time zero to 12 hours post dose at steady state, calculated by using the pre-dose concentration (Ctrough,ss) as the 12 hr concentration, assuming steady-state has been reached (hr*ng/mL).
Cmax,ss	Maximum plasma drug concentration at steady state (ng/mL)
Tmax,ss	Time to reach maximum plasma drug concentration at steady-state (hr)
T1/2,ss (HL)	Elimination half-life associated with the terminal slope of a semi logarithmic concentration-time curve at steady-state (hr)
Ctrough, ss	Steady-state plasma concentration at the pre-dose time for b.i.d. dosing (ng/mL)

[redacted]

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 drug 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 drug 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.”
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IVR system.
Subject number	A number assigned to each patient who enrolls in the study. When combined with the center number, a unique identifier is created for each patient in the study.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment.
Stage	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 drug was discontinued whichever is later.
Study drug	Any drug administered to the patient as part of the required study procedures; includes investigational drug and any control drugs.
Study drug discontinuation	Point/time when patient permanently stops taking study drug for any reason;
Subject	An individual who has consented to participate in this study. The term Subject may be used to describe either a healthy volunteer or a patient.
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints.
Withdrawal of Consent	Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact

Amendment 9 (03-May-2018)

Amendment Rationale

Of the 19 patients initially enrolled under Amendment 4, 10 patients are still ongoing as of 03 May 2018.

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

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

Due to the extension of the study duration, this amendment is classified as substantial.

Changes to the protocol and the ICF

- Protocol synopsis and Sections 3.1, 5.5.15, and 6: Long Term Extension-2 end day changed from 31 December 2018 to 31 December 2019
- Glossary: Updated Personal Data and Withdrawal of Consent language
- Section 5.5.12 Updated Withdrawal of Consent language
- Updates to the ICF include updating the study end date from 31 December 2018 to 31 December 2019 throughout the document and the implementation of General Data Protection Regulation ("GDPR") language for sites in the European Union.

IRB/IEC

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.

[redacted]

Amendment 8 (11-Jul-2017)

Amendment Rationale

Of the 19 patients initially enrolled under Amendment 4, 11 patients are still ongoing in the trial as of 14 June 2017.

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

This protocol amendment introduces the following changes:

1. The End of study (EOS) definition was changed throughout the protocol from "until LCI699 is commercially available and reimbursed or through the availability of a local access program" to "patient treatment in Long Term Extension-2 will end at each site within 4 months after a separate roll-over study is opened at their site, or by 31 December 2018 (whichever occurs earlier). The roll-over study will provide an opportunity of continued treatment for patients who are still ongoing at that time and who are clinically benefitting from LCI699. For sites where a separate roll-over study is not an option, the patient may be offered a local alternative treatment option. In addition, the option of an earlier End of Trial (EOT) visit (i.e. earlier than the 6 month interval visits in Long Term Extension-2) has been implemented to allow seamless transition of patients into the separate rollover study.
2. 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 (Section 3.5).
3. 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®).
4. Section 9.8 (Interim Analysis) was updated to allow for an additional database lock in support of future market authorization applications for LCI699.

Due to the updated EOS definition, this amendment is classified as substantial. Updates to the ICF include addition of EOS definition, information on possible continuation into roll over protocol and updated Novartis wording on data use and protection.

Changes to the protocol

- Protocol Synopsis: Clarification of end of patient study participation.
- Assessment Schedule: New Footnote #6 and #7 under "Long Term Extension-2"

[redacted]

- Section 3.1 Optional Long Term Extension-2: clarification of end of patient participation, option of entry into roll over protocol and EOT/EOS visit completion.
- Section 3.5 Risk/benefit for this study: Update to effects on QTc interval, based on information from LCI699C2105 thorough QT study. Added reference to LCI699 Investigator brochure, for up to date information.
- Section 3.5 Risk/benefit for this study: Update to effects on adrenal hormones.
- Section 5.5.15 Study completion and post-study treatment: clarification for patient's completing LCI699C2201 study or entering roll-over protocol. Added clarification of EOT/EOS visit completion.
- Section 9.8 Interim Analysis: updated to allow for an additional database lock in support of future market authorization applications for LCI699.
- Appendix 6: Removal of table listing medications with a known risk of QTcF prolongation. Provision of e-link to list of drugs to provide access to most up to date information.

IRB/IEC

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.

[redacted]

Summary of previous amendments

Amendment 7

Of the 19 patients initially enrolled under protocol Amendment 4, 12 patients are still ongoing in the trial under the open-ended long term extension as of 30 November 2015.

This protocol amendment introduces the following changes:

- The primary purpose of this protocol amendment is to ensure patient safety by adding specific criteria for the identification and management of patients with potential drug-induced liver injury (DILI). 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.
- Update to the requirement for contraception by male study participants. For male subjects participating in clinical trials, contraception is not required. The rationale is that the safety margin for causing embryo-fetal toxicity and teratogenicity through seminal fluid transfer is > 100-fold. Based on the FDA guidance for Industry (2011), if the compound is teratogenic and/or embryolethal and the safety margin is >25, then male condom use is not required. Given the fact that at the proposed clinical doses of LCI699, there is a sufficient safety margin in causing reproductive, embryofetal, and teratogenic effects via seminal transfer of LCI699 to the potential female partner, male patient contraception is no longer required.
- Clarification of protocol language regarding withdrawal of consent, study drug discontinuation, and discontinuation procedures

In addition, minor editorial changes were applied in the List of Abbreviations.

Changes to the protocol

- List of Abbreviations: Revised to include new terminology introduced in Amendment 7
- Assessment Schedule: Correction to Footnote #2 under “Extension Study” and to Footnote X under “Long Term Extension-2”
- Section 3.5 Risk/benefit for this study: Reference to males was deleted from the “Effects of sex hormones” section
- Section 5.5.5: Added section on Dose modification and dose delay
- Section 5.5.6: Added section “Follow up on potential drug-induced liver injury (DILI) cases
- Section 5.5.9 Prohibited Treatment: Removed “premature” to clarify study discontinuation
- Section 5.5.11 Discontinuation of study treatment: Updated language to define withdrawal of consent and clarify process of discontinuation
- Section 5.5.12 Withdrawal of Consent: Added section to clarify Withdrawal of Consent procedures
- Section 5.5.13 Lost to Follow-Up: Updated template language regarding patients lost to follow-up

[redacted]

- Section 5.5.14 Early Study Termination: Updated template language for clarification
- Section 6: Removed “premature” to clarify study discontinuation

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.

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Boards (IRBs), Independent Ethics Committees (IECs) and Health Authorities.

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

[redacted]

Amendment 6

As of 01 March 2014, 19 patients have been enrolled under protocol Amendment 4 of the protocol. A total of 17 patients completed the 22 week core phase of the study and 2 patients were discontinued. Of the 17 patients who completed the core phase, 16 patients are enrolled in the optional long term extension-1 of the study.

Amendment Rationale

The purpose of this protocol amendment is to continue the study to monitor patients for long-term safety and efficacy, and to provide continued access to LCI699 to patients who have completed long term extension-1. As there are only 16 patients currently participating in extension-1, and the clinical development program of LCI699 is still in its early stage, it is important to continue to collect long-term safety and efficacy data over a longer period of time. In addition, considering that currently available alternative treatment options have limitations to their efficacy and safety profiles, this additional extension (extension-2) will provide patients who are clinically benefitting from LCI699 an opportunity to continue to have access to the drug until LCI699 is commercially available and reimbursed or through the availability of a local access program.

At day 490, the end of long term extension-1, patients will be evaluated by their investigator for clinical benefit. Provided that the investigator's assessment is that the patient would benefit from continued treatment with LCI699, and does not meet the protocol's termination criteria, the patient will have the option to enter a second long term extension period (extension-2), which will continue until LCI699 is commercially available and reimbursed or through the availability of a local access program.

In addition, the protocol has been updated to indicate that the formulation of LCI699 will be changed from capsules to tablets during long term extension-2. The reason for this change is that the tablet formulation will be used in the pivotal Phase III studies of LCI699 and other clinical trials for the treatment of patients with Cushing's disease. LCI699 is considered a BCS class I compound, characterized by its high solubility, high permeability and extensive absorption. For these compounds, as long as the dosage forms have rapid and similar in vitro dissolution profiles, the rate and extent of drug absorption are not expected to be different. Therefore, the two LCI699 formulations (capsule and tablet) are expected to have similar pharmacokinetic properties. Comparative *in vitro* dissolution data will be included in the quality information for the tablets, and no patient will be allowed to switch to the tablet formulation until any necessary approvals are received.

Changes to the protocol

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

Assessment Schedules: Revised to include the additional visits for long term extension-2.

Section 3.1 Study Design: A description of the optional long term extension-2 was added

Figure 3-1: Revised to include the second optional long term extension (extension-2)

[redacted]

Sections 3-2, 3-3 and 3-5: Revised to include the second optional long term extension (extension-2)

Section 5-1: Revised to add the 1, 5, 10 and 20 mg tablets

Section 6.5.1: Revised to include the second optional long term extension (extension-2)

Section 6.5.5: Salivary cortisol and aldosterone: Additional assessment days added during long term extension-2.

6.6.5: Revised to add long –term extension-2

Appendix 1: Revised to be consistent with the long term extension -2 assessments

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.

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Boards (IRBs), Independent Ethics Committees (IECs) and Health Authorities.

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

[redacted]

Amendment 5

As of 01 Apr 2013, 12 patients have been enrolled under protocol Amendment 4 of the protocol and 7 have started treatment. Six patients are still under treatment, 3 patients are under screening, 2 are screen failed and 1 patient has withdrawn due to adverse event.

Amendment rationale

Cardiac safety

1. ECG Monitoring

With this amendment, ECG monitoring will be intensified during the study. The reason for this change is to further enhance patient safety and collect additional safety information because new pre-clinical and preliminary clinical results indicate a potential risk of QTc prolongation in humans. Of note, there have been no QT-related Adverse Events (AEs) reported in the clinical development program of LCI699 to date, in which a total of 659 subjects have been exposed to the drug, and with exposures as single doses of 200 mg, and repeated doses as 50 mg bid.

Preclinical Data

New results from a monkey telemetry study show QTc prolongation, conduction abnormalities, and cardiac arrhythmias at very high exposures to LCI699. In this study, a total of 6 monkeys (3 males and 3 females) sequentially received single oral doses of LCI699 of 10mg/kg, 30mg/kg, and 100mg/kg, while ECG was continuously monitored for a total of 24 hours post-dose.

No ECG abnormalities were observed after the 10mg/kg dose. However, QTc prolongation was observed in 2 male and 1 female animals at an LCI699 dose of 30mg/kg. The lowest plasma free-drug concentration (Cmax) that resulted in QTc prolongation was 13.1 μM, which is approximately 16-times the free-drug steady-state Cmax (0.81 μM) estimated in healthy volunteers at the currently proposed maximum clinical dose of 30 mg bid. Conduction abnormalities, including aberrant ventricular conduction were observed in 1 male animal at 100mg/kg (Cmax 91.1μM, or 112-times the human exposure at the 30 mg dose). PVCs, non-sustained ventricular tachycardia, and a brief, reversible episode of Torsade de Pointe (TdP) were observed in another individual male animal at 100mg/kg (Cmax 176.4 μM, or 217-times the human exposure at the 30 mg dose).

The new results are consistent with prior pre-clinical cardiac safety data. An *in vitro* hERG assay showed evidence of inhibition with IC25=18.9 μM, and IC50=54μM. *In vitro* isolated rabbit heart had an APD60 prolongation at ≥ 1μM, and proarrhythmic indices indicative of a torsadogenic potential at 10 μM.

In vivo cardiovascular safety in dogs showed no QTc change at single or repeat oral doses up to 10mg/kg. However, in a 2-week intravenous LCI699 infusion in dogs at 50mg/kg/day, there was a variable increase in the QRS complex and QTc interval (17% in males, 22% in

[redacted]

females). At 50 mg/kg, the Css was 12.4 μM free-drug, or approximately 15 times the Cmax of 0.81 μM after 30 mg oral dosing in healthy human volunteers.

Preliminary Clinical Data

The new findings in the monkey telemetry study prompted a careful review of all prior ECG data in the LCI699 program. There have been no QTc-related AEs reported in the clinical development program of LCI699 to date, in which a total of 659 subjects have been exposed to the drug. This includes the 12 patients with Cushing's disease that received LCI699 at the 10-week interim analysis of the current study [LCI699C2201]. Although the current study [LCI699C2201] was not designed to control adequately for changes in the QT interval, locally read 12-lead ECGs were performed at baseline and the end of study (EOS) visit. In the 10-week interim analysis, the mean (± SD) for QTcB at screening was 388.60 ± 62.803 msec, and at the end of study (2 weeks after the last dose of LCI699 was administered) was 412.31 ± 28.861 msec. No conclusion can be drawn from these data because of the high variability of results, the absence of correlation with LCI699 plasma concentration, and the potential for several concomitant risk factors for QT prolongation.

Preliminary results from an exploratory post-hoc analysis of data from the Phase I study [LCI699A2101] in healthy volunteers showed evidence of significant QTcF prolongation (> 30ms in some patients) after single doses of 100mg and 200mg, particularly at 2 hours and 4 hours post-dose. However, no QTcF prolongation was observed after a single 30mg dose. These results should be interpreted with caution, because study [LCI699A2101] was not designed to control adequately for changes in the QTcF interval. Nonetheless, it appears that LCI699 does cause QTcF prolongation in humans at least at doses of 100 mg or higher.

Intensive Cardiac Monitoring

Based on the preclinical cardiac safety data, and preliminary clinical data -on QT prolongation from study [LCI699A2101] and [LCI699C2201]-, it is necessary to assess the risk of QT prolongation in patients with Cushing's disease. Therefore patients in the present study will have intensive ECG monitoring to collect additional important safety data and to further enhance patient safety in the clinical trial setting. In addition, a "thorough QT" (TQT) study [LCI699C2105], designed according to the ICH E14 and FDA Guidance (2005), is planned in healthy volunteers. As mentioned above, no QTc-related adverse events have been reported in clinical trials of LCI699 to date.

Intensive cardiac monitoring will include standard 12-lead Safety ECGs and 24-hour continuous 12-lead Holter recordings, as described in Section 6.6.5:

- Safety ECGs will be the primary method of monitoring cardiac safety, and will be performed at each study visit day that LCI699 is administered, as described in section 6.6.5. The safety ECGs are timed to coincide with the Cmax for LCI699 (1.5 hours post-dose), and enable a real-time assessment of QTc at the time the risk of QTcF prolongation is highest. Safety ECGs are to be read by a qualified physician (e.g., the investigator or another qualified physician, such as a consulting cardiologist) immediately to screen for significant abnormalities. A safety algorithm is initiated for any instance that the QTc is > 500ms.

[redacted]

- 24-hour Holter recordings will be performed on 5 days during the study. The data are electronically submitted to a central lab for subsequent analysis. The Holter recordings are NOT intended for real-time feedback of the cardiac rhythm, but instead are for the collection of large amounts of ECG data. When the Holter is performed on the same day that PK profiling is also performed, the PK data will be correlated to the ECG data to evaluate the drug exposure-QTc effect relationship.

2. Concomitant medications that increase QTc

This protocol amendment also provides a list of drugs (see Appendix 6) that are known to cause QT prolongation. With the exception of temporary interruption of study drug therapy because of a short-term need to use a QT-prolonging drug (e.g., certain antibiotics), these drugs are prohibited as concomitant medications in this study, because there is a potential risk of additive QT prolongation with LCI699.

3 Reduction of maximum LCI699 study dose

Another change to enhance patient safety is to remove the highest dosing regimen (50 mg bid) from the dose titration schedule, and add a dose of 30 mg bid for those patients who do not have normalization of UFC at 20 mg bid. The rationale for this change is that the results of the exploratory post hoc analysis of QTcF in relation to LCI699 dose from the phase I study [LCI699A2101] found no evidence of a QTcF prolongation effect after a single 30 mg dose, but did find substantial QTcF changes (some patients with QTcF prolongation > 30 ms) at single doses of 100 mg and 200 mg. Since it is not yet clear at which dose or plasma concentration of LCI699 the threshold for a QT prolongation effect is, the 50 mg bid dose was removed as a precaution.

If at the time this protocol Amendment 5 is implemented, any patients are already treated by the 50 mg bid dose, the dose must be reduced to the new maximum dose of 30 mg bid.

Inclusion and Exclusion Criteria

Radiation therapy

Pituitary irradiation can be used as second-line therapy when trans-sphenoidal surgery has failed to control hypercortisolism. Either conventional pituitary radiation or radiosurgery (gamma-knife therapy) are often effective in this clinical situation. Pituitary irradiation results in slowly declining ACTH secretion by corticotroph adenomas. Based on published data by Estrada et al (1997); Minniti et al (2007); and Losa et al (2010), the time course to normalization of UFC is often within 2-5 years after post-irradiation in about 80% of cases (Estrada et al 1997; Minniti et al 2007; and Losa et al 2010). Some, but relatively few patients respond more than 5 years post-irradiation, and this can be observed up to 10 years post irradiation (Losa et al 2010). In one study (Minniti et al 2007; N=40 patients), normalization of plasma cortisol was seen in 28% of patients at 1 year, 78% at 5 years and 84% at 10 years. Pituitary irradiation often results in permanent hypopituitarism in about 20-40% of patients post-radiation.

Since the effect of radiation has the potential to contribute to the decline and control of the 24-hour urine-free cortisol (UFC), at the same time that the evaluation of this effect by the study drug LCI699 is being assessed, radiation could be a confounding factor in interpreting the primary analysis of the study. Consequently, patients with a history of pituitary irradiation within 5 years prior to study entry are excluded.

Modified definition of escape

One of the secondary objectives is to assess escape (Section 2.2). The definition of escape has been modified to include its relation to the highest tolerated dose of LCI699. The concept of escape refers to loss of control of UFC after having attained normalization of UFC on LCI699 therapy at an earlier time point. In this study, it is permitted to increase the dose of LCI699 not only during the dose titration phase (weeks 1-10), but also during the treatment period (weeks 11-22) of the core study, and during the extension study if applicable. This is intended to mimic clinical practice. The additional requirement to have uncontrolled UFC at the highest tolerated dose of LCI699 is also intended to reflect anticipated clinical use of the drug. The highest tolerated dose is the highest dose without a drug-suspected adverse event (AE), up to the maximum LCI699 dose of 30mg bid.

The requirement of uncontrolled UFC on two consecutive visits is intended to ensure that the elevated UFC is not due to lab error or variations just above the upper limit of the normal reference range. Escape events will be described by a Kaplan-Meier analysis of "time to escape," i.e., the time (in weeks) from the first normalization of UFC to the first of two consecutive uncontrolled UFC levels (Section 9.5.2).

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 changes throughout the protocol.

Assessment Schedules: Table has been updated to reflect the intensive cardiac monitoring (ECG and Holter) and the additional interim visits when dose escalation should occur if needed.

Section 1.1.1.1 (Table 1-1): Safety margin multiples for the 30 mg bid dose have been added to Table 1-1.

Section 1.1.1.4: This section has been updated to include estimation of PK exposure at 30 mg bid, and added background on emerging preclinical data regarding LCI699 metabolism.

Section 2.2: Secondary objective on escape, and the definition of escape, were modified.

Section 3.1: Addition of the interim dose escalation visits and update of Figure 3-1 to reflect new design with interim visits. Section updated (including Figure 3-1) to reflect the change of the maximum dose strength of 30 mg.

Section 3.5: Risk/benefit section updated including effect on QTc interval, minor editorial changes and providing clarification regarding effects of sex hormones.

Section 4.1: Inclusion criteria for confirmation of pituitary origin of excess ACTH has been modified with respect to Inferior Petrosal Sinus Sampling (IPSS).

Section 4.2: Exclusion criteria were added (pituitary irradiation and risk factors for QTc prolongation or Torsade de Pointes).

Section 5.5.7: Addition of a list of prohibited treatments related to potential risk of QTc prolongation.

Section 5.5.8: Based on emerging preclinical data, CYP3A4/5 and CYP2D6 may be involved in the metabolism of LCI699. As such, a list of comedications to be used with caution with LCI699 due to potential risk of drug-drug interactions is added.

Section 5.5.9: Addition of discontinuation criteria.

Section 6: Clarification on sequence of assessments and addition of visit window.

Section 6.5: Missing assessments were added to list.

Section 6.6.5: Section has been updated to reflect the details of intensive cardiac monitoring (12-lead Safety ECG and 24-hour Holter recording) as well as to include the QT prolongation algorithm.

Section 6.7.1.1: A few PK collection times referenced in this section and in Table 6-2 were incorrect. These have now been corrected.

Section 9.5.2: Missing escape analysis has been added to analysis of secondary variables.

Section 9.5.8: QTcF has been added to PK/PD correlation analysis.

Appendix 1: Time for visit 2 sample log has been extended to baseline period (day-14 to day0) in order to have all results available to check inclusion/exclusion criteria before day1.

Appendix 6: Appendix 6 was added to list drugs with a known risk of causing QT prolongation.

Appendix 7: Appendix 7 was added to list drugs that are strong CYP3A4/5 and CYP2D6 inhibitors and inducers, to be used with caution as concomitant medications with LCI699

IRB/IEC

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. In addition, the changes herein affect the Informed Consent and sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

[redacted]

Amendment 4

Amendment rationale

As of 10 Feb 2012, 12 patients have been enrolled in the study and 11 have completed the core period of 10 weeks. One patient is ongoing and is scheduled to complete the 10 weeks in March 2012.

Preliminary data as of Dec 2011 from the present study in 11 out of the 12 subjects with Cushing's disease were evaluated. Of these, 9 had completed and 2 were still ongoing. LCI699 normalized UFC on at least 1 assessment in 11 out of 11 subjects during the study (baseline UFC range of 1.6-17.0xULN). The primary endpoint was achieved by all 9 subjects who had completed the active treatment phase (10 weeks), 8 of whom had normal UFC levels on day 70. A mean increase in plasma ACTH (2-3 fold) was observed from baseline to week10.

The dose at which patients achieved normalization of UFC varied; Overall, all 11 patients had at least one UFC <ULN in recorded visits. One patient had normal UFC with a dose of 2 mg bid, 3 patients had normal UFC with a dose of 5 mg bid, 3 patients had normal UFC with a dose of 10 mg bid, one patient had normal UFC with a dose of 15 mg bid, two patients had normal UFC with a dose of 20 mg bid and one patient had a normal UFC with a dose of 50 mg bid.

LCI699 was generally well tolerated. There were no discontinuations due to adverse events or serious AEs of suspected drug relationship reported. Eleven patients reported at least one AE. Additional information from the data cut is presented in Section 1.1.1.3.

The purpose of this protocol amendment is to confirm the preliminary observations from this proof of concept (PoC) study by enrolling a new cohort (Expansion cohort) of patients and evaluating the long-term efficacy and safety of LCI699 treatment for a total duration of 22 weeks. This longer treatment period will help address questions on the sustainability of the cortisol reductions and longer term safety (e.g. potential on ACTH levels and off-target effects on the mineralocorticoid and androgen pathways). At the end of the 22 weeks, patients will have the option to enter into the long term extension for duration up to 12 months.

With this amendment, approximately 15 new patients (not previously enrolled) with Cushing's disease will be enrolled as the "Expansion Cohort". Patients who previously completed the trial prior to Amendment 4 and benefited from the treatment with LCI699 will also be allowed to re-enter the study as the "Core PoC Follow-up Cohort". These patients will start the study over again at screening and follow through the visit schedule the same as new patients. Core PoC Follow-up patients can reenter if their UFC is > ULN and all other eligibility criteria have been met.

Rationales for changes in this amendment are presented below:

Sample size

To confirm the preliminary observations, additional patients will be enrolled. In view of the rarity of Cushing's disease 15 additional patients was chosen based on practical

[redacted]

considerations. The 12 patients who participated in the trial prior to Amendment 4 are also allowed to restart the study at screening and will be in addition to the 15 new patients.

Treatment duration

The original protocol limited treatment duration of 10 weeks. In order to better understand the long-term efficacy and safety profile of LCI699 the total treatment duration with LCI699 will be extended to 22 weeks.

PK blood sampling

Current multiple dose PK data of LCI699 are limited to healthy volunteers who received significantly lower doses (3 mg qd and 1 mg bid) than doses being used in Cushing's disease in the core PoC study (2, 5, 10, 20 and 50mg bid). In addition, PK sampling in Cushing's disease patients prior to Amendment 4 was limited to trough samples only. Therefore, further PK sampling (0 to 6 hrs post-dose) is needed to determine steady state PK parameters such as Cmax, Tmax, AUC0-6hr, AUC0-12hr (utilize Ctrough at steady state as concentration at 12hr post dose), T1/2 and Ctrough at doses that are more relevant in the target population (i.e., 2-50mg bid), particularly in view of over-proportionality findings in healthy volunteers. In addition, PK/PD analysis based on those PK parameters will be better than using trough concentrations to define the dose/exposure and exposure/efficacy relationship, and eventually to facilitate the design of future registration trial as well as to build a population PK/PD model of LCI699 in Cushing's disease patients. Therefore, the 6-hr PK blood sampling will be added during the initial 10-week dose titration phase to characterize the steady-state pharmacokinetics of LCI699 at each dose level in Cushing's disease patients.

LCI699 starting dose

Preliminary results from this study showed that the median dose of LCI699 associated with UFC normalization was between 5 and 10mg bid. In view of the need to obtain more rapid control in patients with severe hypercortisolism, patients with baseline mUFC > 3xULN will not undergo the initial 2 week treatment with LCI699 2 mg bid, and will instead be started on the 5 mg bid dose.

Study assessments

Additional study assessments and changes include the use of a central lab, Pituitary MRI, and plasma lipid profile. Further, home BP monitoring and salivary assessments have been modified.

Central lab

- Use of a central laboratory is deemed necessary to standardize key assessments related to LCI699 action across the study sites and will be done for the following analytes: UFC, plasma cortisol, plasma ACTH, salivary cortisol and aldosterone, 11-deoxycortisol, plasma and urine deoxycorticosterone, plasma and urine aldosterone, plasma renin, PK, testosterone and estradiol, LH, FSH, IGF-1. Local labs can be used throughout the study for dose titrations and/or if a faster turnaround time is needed for safety reasons.

Pituitary MRI

- Pituitary MRIs are added to assess potential corticotroph tumor progression in patients with Cushing's disease as a result of cortisol synthesis inhibition/adrenal blockade with LCI699 monotherapy. MRIs will be performed at screening/baseline and at week 22. MRI's will be read locally. Digital images are to be kept at the site in the event Novartis requests transfer of the files at a later date. Details on images and acquisition can be found in the Study Imaging Manual.

BP and Salivary assessments

- Daily home BP monitoring is no longer deemed necessary based on the initial PoC results and is being removed to reduce undue burden on patients.
- In addition, the twice daily determinations of salivary cortisol and aldosterone are not deemed necessary and therefore the frequency has been reduced to weekly.

Lipid Assessments

- Due to the potential androgenic effect of LCI699 (and atherogenic lipid changes), a full lipid profile has been added to each visit and will include TC, TG, HDL-cholesterol and LDL-cholesterol.

Optional study extension

- Considering that no approved medical therapy exists and alternative treatment options are limited due to lack of response and/or side effects, the extension provides these patients, responding to LCI699, an opportunity to continue treatment while generating long term safety and efficacy data.
- At the end of week 22, patients will be evaluated for clinical benefit and have the option to enter the 12 month long term extension phase at the investigators discretion provided they do not meet discontinuation criteria.

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. The changes being made to the protocol due to this amendment are incorporated in the following sections:

- Throughout the protocol, the term subject has been updated to the term patient for consistency. The term subject was left only if discussing a healthy volunteer.
- Title Page: The title has been updated to show the longer treatment period.
- List of abbreviations, Pharmacokinetic definitions and symbols, and Glossary of terms: these tables have been updated based on changes throughout the protocol.
- Amendment 4 section: Added to describe changes introduced with amendment 4
- Protocol Synopsis: edited to be consistent with changes throughout the protocol.
- Assessment Schedules: A new assessment schedule has been created to avoid confusion. The additional visits and the 12 month extension have been added as well as the PK and MRI.

- Section 1.1: editorial changes made as well as addition of preliminary data from this study.
- Section 1.1.1.1: editorial changes made.
- Section 1.1.1.3: addition of preliminary data from this study.
- Section 1.1.1.5: addition of preliminary data from this study.
- Section 1.2: study purpose updated to include addition of new cohorts and 12 month extension.
- Section 2.2: secondary objectives added for the new cohorts.
- [redacted]
- Section 3.1: the study design was updated with instructions for the 2 different cohorts and for the additional visits.
- Figure 3-1: updated for the new design and additional visits.
- Section 3.2: Rationale added for the additional 12-week treatment period and for the 12-month extension.
- Section 3.3: Rationale added for the additional 12-week treatment period, the 12-month extension and the 5mg starting dose in severe patients.
- Section 3.5: The potential benefits and risks sections have been updated with preliminary data from this study.
- Section 3.6: the interim analysis plans have been updated.
- Section 4: this section has been updated to include information on the 2 new cohorts.
- Section 4.1: The inclusion criteria 3 was updated to include criteria for patients in the core PoC follow-up criteria, criteria 4 was added to include patients with de novo only when non candidates for surgery and mifepristone was added as a washout medication to criteria 5.
- Section 4.2: Exclusion criteria 5 and 6 for the pregnancy guidelines have been updated based on standard practice at Novartis. Criteria 11 has been updated to include specific information for excluding pseudo-Cushing's syndrome.
- Section 5.2: The starting dose has been updated to include 5 mg for severe patients.
- Section 5.5.1: Addition of the Patient number for the 2 new cohorts.
- Section 5.5.5: sentence deleted stating rescue medication recording process as there is no rescue medication.
- Section 5.5.6: language clarified for capture of concomitant medications starting at signing of informed consent.
- Section 5.5.9: removed the symptomatic hypotension criteria and added hypokalemia criteria.
- Section 5.5.11: removed sentence referring to treatment continuation in a separate protocol.
- Section 6: statement added for visit times to be consistent, added end of treatment visit and end of study visit.
- Section 6.1: added procedures for screening visit.
- Section 6.2: added fasting information and PK-profile meal timing.
- Section 6.5: added parameters assessed by the central laboratory.

[redacted]

- Section 6.5.1: mean Urinary free cortisol assessment timing changed and reference to the assessment schedule added.
- Section 6.5.1.1: Central laboratory added.
- Section 6.5.1.2: Central laboratory added.
- Section 6.5.2: reference to the assessment schedule added.
- Section 6.5.3: reference to the assessment schedule added.
- Section 6.5.4: reference to the assessment schedule added.
- Section 6.5.5: timing of the salivary samples updated and reference to the assessment schedule added.
- Section 6.5.6: reference to the assessment schedule added.
- Section 6.6.1: reference to the assessment schedule added.
- Section 6.6.2: reference to the assessment schedule added and the home blood pressure monitoring removed.
- Section 6.6.3: reference to the assessment schedule added.
- Section 6.6.4.2: lipid parameters added.
- Section 6.6.5: reference to the assessment schedule added.
- Section 6.6.6: added section to discuss MRI procedures.
- Section 6.6.7: reference to the assessment schedule added.
- Section 6.7.1: updated section to include instructions on the PK profiling.
- Section 6.7.3: statement regarding remaining samples added.
- [redacted]
- Section 7.1: adverse event reported changed to start from informed consent signing.
- Section 7.3: statement added regarding pregnancy outcomes for female partners of male patients.
- Section 8.3: Obvious error correction removed as this is no longer performed. Also removed reference to paper CRFs as the study uses EDC.
- Section 9.1: analysis sets defined for the additional cohorts.
- Section 9.2: analysis further defined for demographic data.
- Section 9.3: analysis further defined regarding treatment.
- Section 9.4: Primary variable clarified for applicable cohort.
- Section 9.4.1: analysis further defined by controlled and partially controlled.
- Section 9.4.2: statistical method updated.
- Section 9.5.1: additional cohorts added.
- Section 9.5.3: analysis defined for the cohorts.
- Section 9.5.5: stead state PK parameters added.
- Section 9.5.8: statistical method updated and added that PK/PD analyses may be done separately.

[redacted]

- Section 9.6: statement regarding expansion cohort effect on the precision of the responder rate added.
- Section 9.8: Interim analyses updated.
- Appendix 1: updated based on additional visits and samples.
- Appendix 2: updated to incorporate labels being provided by the central laboratory.

IRB/IEC/REB Approval

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

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

Amendment 3

Amendment rationale

The purpose of this protocol amendment is to revise and clarify the statistical analysis that will occur at the end of the study. In addition, the need for a urinary free cortisol measurement at screening has also been removed to reduce undue burden to the patients.

Changes to the protocol

- Removal of the urinary free cortisol measurement at screening. This will be implemented throughout the protocol.
- Clarification of the statistical method of analysis, the handling of missing values and the sample size calculation. This will be implemented throughout 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.

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. In addition, if 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 amended protocol.

This amendment will take effect after study start.

Amendment 2

Amendment rationale

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

This amendment will take effect prior to study start.

Changes to the protocol

- Changes in blood volume required for Pharmacodynamic assessments. See Appendix 1.

Amendment 1

Amendment rationale

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

This amendment will take effect prior to study start.

Changes to the protocol

- Clarification that only subjects with a confirmation of pituitary origin of excess ACTH will be included. See Section 4.1
- Additional exclusion criteria concerning subjects with adrenal Cushing's syndrome and pseudo-Cushing's syndrome. See Section 4.1
- Responders will now be defined as having a normalization of UFC or a ≥50% decrease in UFC. This will be implemented throughout the protocol.
- Addition of a dose adjustment decrease for subjects with symptomatic hypocortisolism. See Section 5.5.4
- Changes in study stopping rules to unexpected drug related AEs. See Section 5.5.9.
- The assumptions and power calculations to support the study sample size have been revised. Consequently, the originally planned interim analysis has been removed. This will be implemented throughout the protocol.
- Removal of the Karnofsky performance status as not deemed relevant upon further reflection. This will be implemented throughout the protocol.
- Addition of saliva sample collection throughout the baseline and wash-out periods of the study. This will be implemented throughout the protocol.
- Removal of an extension study. This will be implemented throughout the protocol.
- Removal of the PK sample at Day 84 as trough sample collection not needed 14 days after last dose of study drug. This will be implemented throughout the protocol.
- Clarification on timing of PD sample collection and additional PD parameters to allow further analysis surrounding secondary objectives. This will be implemented throughout the protocol.
- Clarification of the urine and blood sample log to reflect PD sample numbering and addition of a saliva log to allow for sample numbering.

[redacted]

- Increase in total blood volume from 196.5ml to 244ml due to addition of pharmacodynamic samples.
- Missing data will now be imputed using LOCF. See Section 9.4.3

[redacted]

Protocol synopsis

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

Purpose and rationale: This exploratory study is designed as a proof of concept of LCI699 in patients with Cushing's disease. The purpose of this study is to determine whether the ability of LCI699 to inhibit 11β-hydroxlase can safely reduce urinary free cortisol (UFC) in patients with Cushing's disease. In addition, this study will evaluate an optional 12 month long term extension (long term extension-1) and a second optional long term extension (long term extension-2).

Objectives:

Primary Objective:

To assess the effects of 10 weeks treatment of LCI699 on 24 hour urine free cortisol (UFC) in patients with Cushing's disease.

Secondary Objectives:

- To assess the 10 week safety and tolerability of multiple doses of LCI699 in patients with Cushing's disease
- To assess the 22 week safety and tolerability of multiple doses of LCI699 in patients with Cushing's disease.
- To assess the effect of LCI699 on steroid hormones of the HPA-axis in plasma, urine and saliva
- To assess the effects of LCI699 on improving the metabolic abnormalities (hypertension, dyslipidemia, obesity, insulin sensitivity, HbA1c and FPG) of Cushing's disease
- To assess the steady state pharmacokinetics of LCI699 in patients with Cushing's disease.
- To assess the effect of 22 weeks of treatment with LCI699 monotherapy on 24 hour urine free cortisol (UFC) in patients with Cushing's disease. The proportion of patients with controlled or partially controlled will be determined as follows:
  - Controlled UFC: defined as a mean UFC level ≤ ULN
  - Partially controlled UFC: defined as a mean UFC level > ULN but with ≥50% reduction from baseline.
- To assess escape. Escape is defined as loss of UFC control (i.e. UFC > ULN) on at least 2 consecutive visits at the highest tolerated dose, after previously attaining UFC normalization.

Study design: This is a proof of concept, open-label, single arm, sequential dose-escalation, multi-center study to assess the safety/tolerability and efficacy of 10-weeks treatment of LCI699 followed by a 12 week treatment period in patients with Cushing's disease.

The study will consist of a screening period of up to 60 days (to allow an adequate washout period for any medications that modify cortisol levels), a 10-14-day baseline period, a 10-week treatment period with sequential dose escalation, a 12 week LCI699 BID treatment period where patients will continue to receive LCI699 at the last efficacious dose. Patients will also have the option to enter two long term extensions (long term extension-1 and long term extension-2). Patients will have a Study Completion evaluation approximately 28 days after the last drug administration.

[redacted]

*Note: Patients with baseline UFC > 3xULN will start at 5 mg bid (in lieu of 2 mg bid)

Long Term Extension-2 will end at each site within 4 months after a separate roll-over study is opened at their site, or by 31 December 2019 (whichever occurs earlier). The roll-over study will provide an opportunity of continued treatment for patients who are still ongoing at that time and who are clinically benefitting from LCI699. Sites with the separate roll-over study option available, should arrange their patient's End of Treatment (EOT) visit within 4 months of the roll-over study being opened at their site (i.e. earlier than the 6 month visit intervals in Long-Term Extension-2), to allow their patients to continue their LCI699 dose on this new study.

Patients not continuing into the roll-over protocol will complete an EOT visit upon stopping treatment, and an EOS visit 28 days after the last dose administration, must be completed by 31 December 2019.

Population:

The study population will be comprised of male and female patients with endogenous hypercortisolism due to increased ACTH production from the pituitary (Cushing's disease). Approximately 15 patients (not previously enrolled into the trial) with Cushing's disease will be enrolled to participate in the study. At least 8 patients are expected to complete the study. Patients who previously completed the study prior to Amendment 4 and benefited from treatment with LCI699 will be allowed to re-enter the study at screening if their UFC is > ULN and all other eligibility criteria have been met.

Inclusion/Exclusion criteria:

Inclusion:

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:
   - UFC >1.5XULN (Mean value of three 24-hour urine samples collected within 14 days) [For Patients who completed the first 10 weeks of treatment prior to Amendment 4, the appropriate washout of medical treatment for Cushing's disease has to be followed per inclusion criteria 5. These patients must have UFC >1 X ULN (Mean value of three 24-hour urine samples collected within 14 days).]
   - Morning plasma ACTH above lower limit of normal
   - Confirmation of pituitary origin of excess ACTH by at least one of the following three:

     i) History of MRI confirmation of pituitary adenoma (greater than or equal to 6 mm) with positive dynamic test (e.g. CRH or high dose dexamethasone suppression test)

     or

     ii) History of inferior petrosal sinus sampling in patients with a tumor less than 6 mm that meet any of the following criteria with either CRH or DDAVP (desmopressin) stimulation:

     a) Central to peripheral ACTH ratio ≥ 2 at pre-stimulation baseline, or

     b) Central to peripheral ACTH ratio ≥ 3 after CRH stimulation.

     or

     iii) Prior pituitary surgery with histopathology confirming an ACTH staining adenoma

[redacted]

- Patients are permitted to washout current drug therapy to meet these entry criteria if they have a known diagnosis of Cushing's disease.

4. Patients with de novo Cushing's disease can be included only if they are not considered a candidate for surgery (e.g. poor surgical candidates, surgically unapproachable tumors, patients who refuse to have surgical treatment or surgical treatment is not available)

5. For patients on medical treatment for Cushing's disease the following washout periods must be completed before baseline efficacy assessments are performed

- Inhibitors of steroidogenesis (ketoconazole, metyrapone): 1 week
- Dopamine agonists (bromocriptine, cabergoline), PPAR-gamma agonists (rosiglitazone or pioglitazone): 4 weeks
- Octreotide LAR, Pasireotide LAR and Lanreotide autogel: 8 weeks
- Mifepristone, Lanreotide SR: 4 weeks
- Octreotide and Pasireotide (immediate release formulation): 1 week
- Other experimental therapy: at least 5 half-lives

Exclusion:

1. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives 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 any of the study drugs 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. Pregnant or nursing (lactating) women
5. 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:
   - 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
   - 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 oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
   - 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.
   - 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,
     d) In case of use of oral contraception women should have been stabile on the same pill for a minimum of 3 months before taking study treatment.
6. Fertile males, defined as all males physiologically capable of conceiving offspring UNLESS they use a condom during intercourse while taking the study medication and for 1 week after stopping study medication and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid (criterion no longer applicable as of Protocol Amendment 07).

[redacted]

7. Patients who have been treated with mitotane during the last 6 months prior to Visit 1.
8. Patients with compression of the optic chiasm, in order to exclude patients with a tumor causing chiasmal compression requiring surgery.
9. Patients who have a known inherited syndrome as the cause for hormone over secretion (i.e. Carney Complex, McCune-Albright syndrome, MEN-1, AIP)
10. Patients with Cushing's syndrome due to ectopic ACTH secretion or adrenal Cushing's syndrome
11. Patients with pseudo-Cushing's syndrome (for patients with a mean UFC< 3x ULN further testing to rule out this condition will be required unless Cushing's disease is confirmed by histopathology. At least 2 of 3 tests should be abnormal in order to exclude pseudo-Cushing's: low-dose dexamethasone suppression test, dexamethasone-CRH test or late-night salivary or serum cortisol.
12. Patients with renal impairment (estimated creatinine clearance < 60 mL/min by the MDRD formula), serum creatinine >2.0 X ULN.
13. Patients who are not biochemically euthyroid.
14. Patients who have undergone major surgery within 1 month prior to screening.
15. Diabetic patients with poorly controlled diabetes as evidenced by HbA1C >9%.
16. Patients who have congestive heart failure (NYHA Class III or IV), unstable angina, sustained ventricular tachycardia, clinically significant bradycardia, advanced heart block, history of acute MI less than one year prior to study entry or clinically significant impairment in cardiovascular function.
17. Patients with liver disease such as cirrhosis, chronic active hepatitis, or chronic persistent hepatitis, or patients with ALT/AST more than 3 X ULN, serum bilirubin >2.0 X ULN.
18. 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.
19. Patients who have a history of alcohol or drug abuse in the 6 month period prior to treatment.
20. 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.
21. Patients who have received pituitary irradiation within five years prior to Visit 1.
22. Patients with risk factors for QTc prolongation or Torsade de Pointes, i.e. patients with a baseline QTcF > 470ms, hypokalemia, hyperkalemia, hypomagnesemia, uncontrolled hypothyroidism, personal or family history of long QT syndrome, or concomitant medications known to prolong the QT interval.

Investigational and reference therapy: This study has only one treatment arm; LCI699. Patients will start on a dose of either 2 mg bid if baseline mUFC is ≤ 3 x ULN or 5 mg bid if baseline mUFC is >3xULN and they will increase their dose every 2 weeks until week 10. Patients who previously completed the trial prior to Amendment 4 will start at the penultimate dose and uptitrate as needed over 1 week and then will continue treatment adjusting the dose as needed until week 10. All patients will continue LCI699 treatment from week 10-22.

Efficacy / pharmacodynamic assessments: Efficacy assessments will include urinary free cortisol, plasma ACTH, cortisol, 11-deoxycortisol and renin, plasma and urine deoxycorticosterone, plasma and urine aldosterone, serum and urine sodium and potassium, salivary cortisol and aldosterone, testosterone and estradiol, LH, FSH, IGF-1, TSH, free T4, HbA1c and plasma insulin.

Safety assessments: Safety assessments will include physical examinations, 12-lead Safety ECGs, 24-hour continuous 12-lead Holter recordings, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, serum lipids, urinalysis), blood and urine hormones, adverse events, serious adverse event monitoring and pituitary MRIs.

Pharmacokinetic assessments: Pharmacokinetic assessments for LCI699 will include 0 to 6-hr PK samples at the steady state of each dose escalation up to week 10, as well as trough samples up to week 22.

[redacted]

[redacted]

Data analysis: The primary variable is defined as the proportion of responders to LCI699 at Week 10. A patient is considered to be a responder if the mean UFC level from the Week 10 24-hour urine samples is ≤ ULN or represents a ≥50% decrease from baseline. Patients who discontinue for a disease or treatment related reason (e.g. death, adverse event, clinical disease progression etc.), or whose mean Week 10 24-hour UFC levels are higher than the normal limit and whose decrease in UFC is < 50%, are classified as non-responders. Patients who have <2 baseline or post-baseline 24-hour UFC measurement will not be included in the primary analyses.

The proportion of responders and the associated 95% confidence interval will be estimated using the Exact Binomial Test.

[redacted]

Assessment schedules

Core study

	Category	Screening	Baseline	Dose Escalation Period											12 week treatment period		EOT CORE	EOS 28 days post last dose[8]
Visit Number		**V1**	**V2**	**V3**	**V4**	**V5**	**V505**	**V6**	**V605**	**V7**	**V705**	**V8**	**V805**	**V9**	**V10**	**V11**	**V777**	**V778**
Days		**D-74 to -15**	**D-14 to 0**	**D1**	**D7**	**D14**	**D21**	**D28**	**D35**	**D42**	**D49**	**D56**	**D63**	**D70**	**D98**	**D126**	**D154**	
Weeks					**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**14**	**18**	**22**	
Informed consent	D	x																
Inclusion/Exclusion criteria	D	x	x															
Relevant medical History/Current medical conditions	D	x																
Demography	D	x																
Physical examination	S	x	x			x		x		x		x		x	x	x	x	x
Pregnancy test[7]	D	x	x	x		x		x		x		x		x	x	x	x	x
Drug administration record - LCI699	D			x		x	x	x	x	x	x	x	x	x	x	x		
Body height	D	x																
Body weight	D	x	x	x		x		x		x		x		x	x	x	x	x
Body temperature	D	x	x											x			x	x
Blood pressure/Pulse rate[1]	D	x	x	x		x		x		x		x		x	x	x	x	x
12 Lead safety ECG assessment	D		x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
12-Lead 24-hour Holter ECG recording	D		x			x								x			x	x
Pituitary MRI	D		x														x	
Hematology, Blood chemistry, Urinalysis	D	x	x	x		x		x		x		x		x	x	x	x	x
IGF-1, TSH, free T4, LH, FSH	D		x											x	x	x	x	x

[redacted]

	Category	Screening	Baseline	Dose Escalation Period											12 week treatment period		EOT CORE	EOS 28 days post last dose[8]
Visit Number		**V1**	**V2**	**V3**	**V4**	**V5**	**V505**	**V6**	**V605**	**V7**	**V705**	**V8**	**V805**	**V9**	**V10**	**V11**	**V777**	**V778**
Days		**D-74 to -15**	**D-14 to 0**	**D1**	**D7**	**D14**	**D21**	**D28**	**D35**	**D42**	**D49**	**D56**	**D63**	**D70**	**D98**	**D126**	**D154**	
Weeks					**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**14**	**18**	**22**	
HbA1C	D		x											x			x	
Testosterone/estradiol	D	x	x			x		x		x		x		x	x	x	x	x
LCI699 PK blood collection	D					x[4]		x[5]		x[5]		x[5]		x[5]	x[6]	x[6]	x[6]	
Urinary Free Cortisol and urine creatinine[3]	D		x		x	x		x		x		x		x	x	x	x	x
Plasma ACTH, cortisol, 11-deoxycortisol and renin	D		x			x		x		x		x		x	x	x	x	x
Plasma and urine aldosterone	D		x			x		x		x		x		x	x	x	x	x
Urine sodium/potassium	D		x	x		x		x		x		x		x	x	x	x	x
Salivary Cortisol and aldosterone[2]	D		x	x	x	x		x		x		x		x	x	x	x	x
Plasma and urine Deoxycorticosterone	D		x			x		x		x		x		x	x	x	x	x
Insulin	D		x			x		x		x		x		x	x	x	x	x
Adverse Events	D	As required																
Prior and Concomitant meds/Therapies	D	As required																
Study completion information	D																	x
End of Treatment information	D																x	

Visit assessments window is ± 2 days.
1= Blood pressure to be measure in seated position after 3 mins resting.
2= To be collected every week in the morning and evening. See Section 6.5.5.
3= Three 24-hour urine collections should be taken within the 4 days prior to visit day (except for baseline: samples should be taken within 7 days prior to day-7).
4= PK samples to be collected at pre-dose(0 hour), 1, 1.5, 2, 4 and 6 hours post AM dose.
5= PK samples to be collected at (1) pre-dose(0 hour), 1, 1.5, 2, 4 and 6 hours post AM dose for escalation dose or (2) pre-dose (trough) for maintained dose.
6= PK sample to be collected at trough (pre-dose) only
7= Pregnancy test at screening, baseline and EOS to be serum.
8= This visit is only for patients not entering the extension.

[redacted]

Extension study

	Category	LONG TERM EXTENSION-1								EOT EXTENSION-1	EOS 28 days post last dose[6]
Visit Number		**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V777**	**V778**
Days		**D154**	**D182**	**D210**	**D238**	**D266**	**D294**	**D322**	**D406**	**D490**	
Weeks		**22**	**26**	**30**	**34**	**38**	**42**	**46**	**58**	**70**	
Physical examination	S		x	x	x	x	x	x	x	x	x
Pregnancy test [4]	D		x	x	x	x	x	x	x	x	x
Drug administration record - LCI699	D	x	x	x	x	x	x	x	x		
Body weight	D		x	x	x	x	x	x	x	x	x
Body temperature	D									x	x
Blood pressure/Pulse rate [1]	D		x	x	x	x	x	x	x	x	x
12 Lead safety ECG assessment	D	x			x			x	x	x	x
Pituitary MRI	D							x[5]		x	
Hematology, Blood chemistry, Urinalysis	D		x	x	x	x	x	x	x	x	x
IGF-1, TSH, free T4, LH, FSH	D		x	x	x	x	x	x	x	x	x
HbA1C	D				x		x	x	x	x	
Testosterone/estradiol	D		x	x	x	x	x	x	x	x	x
Urinary Free Cortisol and urine creatinine [3]	D		x	x	x	x	x	x	x	x	x
Plasma ACTH, cortisol, 11-deoxycortisol and renin	D		x	x	x	x	x	x	x	x	x
Plasma and urine aldosterone	D		x	x	x	x	x	x	x	x	x
Urine sodium/potassium	D		x	x	x	x	x	x	x	x	x
Salivary Cortisol and aldosterone [2]	D		x	x	x	x	x	x	x	x	x
Plasma and urine Deoxycorticosterone	D		x	x	x	x	x	x	x	x	x
Insulin	D		x	x	x	x	x	x	x	x	x
Adverse Events	D	As required									

[redacted]

	Category	LONG TERM EXTENSION-1								EOT EXTENSION-1	EOS 28 days post last dose[6]
Visit Number		**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V777**	**V778**
Days		**D154**	**D182**	**D210**	**D238**	**D266**	**D294**	**D322**	**D406**	**D490**	
Weeks		**22**	**26**	**30**	**34**	**38**	**42**	**46**	**58**	**70**	
Concomitant meds/Therapies	D	As required									
Comments	D	As required									
EOT Extension -1	D									x	
Study completion information	D										x

Visit assessments window is ± 2 days.
1= Blood pressure to be measure in seated position after 3 mins resting.
2= To be collected every 28 days until D322 and then every 3 months at D406 and D490 in the morning and evening. See Section 6.5.5.
3= Two 24-hour urine collections should be taken prior to visit day, 24-hr urine collections.
4= Pregnancy test at EOS to be serum.
5= Macroadenoma patients only.
6 = This visit is only for patients that have completed long term extension-1 and are not entering long term extension-2.

	Category	LONG TERM EXTENSION-2[x]			EOT EXTENSION-2[6]	EOS 28 days post last dose[7]
Visit Number		**20**	**21-26**	**27,28,29…**	**V777**	**V778**
Months[x]		**16**	**Every 3 months**	**Every 6 months**		
Physical examination	S		x	x	x	X
Pregnancy test [4]	D		x	x	x	X
Drug administration record - LCI699	D	X	x	x		
Body weight	D		x	x	x	X

[redacted]

	Category	LONG TERM EXTENSION-2[x]			EOT EXTENSION-2[6]	EOS 28 days post last dose[7]
Visit Number		**20**	**21-26**	**27,28,29…**	**V777**	**V778**
Months[x]		**16**	**Every 3 months**	**Every 6 months**		
Body temperature	D		x	x	x	X
Blood pressure/Pulse rate [1]	D		x	x	x	X
12 Lead safety ECG assessment	D		x	x	x	X
Pituitary MRI[5]	D		X[5]	X[5]	x	
Hematology, Blood chemistry, Urinalysis	D		x	x	x	X
IGF-1, TSH, free T4, LH, FSH	D		x	x	x	X
HbA1C	D		x	x	x	
Testosterone/estradiol	D		x	x	x	X
Urinary Free Cortisol and urine creatinine [3]	D		x	x	x	X
Plasma ACTH, cortisol, 11-deoxycortisol and renin	D		x	x	x	X
Plasma aldosterone	D		x	x	x	X
Urine sodium/potassium	D		x	x	x	X
Salivary Cortisol and aldosterone [2]	D		X	x	x	X
Plasma and urine Deoxycorticosterone	D		x	x	x	X
Insulin	D		x	x	x	X
Adverse Events	D	As required	As required	As required	As required	
Concomitant meds/Therapies	D	As required	As required	As required	As required	

[redacted]

	Category	LONG TERM EXTENSION-2[x]			EOT EXTENSION-2[6]	EOS 28 days post last dose[7]
Visit Number		**20**	**21-26**	**27,28,29…**	**V777**	**V778**
Months[x]		**16**	**Every 3 months**	**Every 6 months**		
Comments	D	As required	As required	As required	As required	
End of Treatment (Extension-2)	D				X	
Study Completion	D					X

Visit assessments window is ± 2 days.

1= Blood pressure to be measure in seated position after 3 mins resting.
2= To be collected every 3 months for the first 18 months and every 6 months until EOT Extension-2 in the morning and evening. See Section 6.5.5.
3= Two 24-hour urine collections should be taken prior to visit day, 24-hr urine collections.
4= Pregnancy test at EOS to be serum.

5 = MRIs will be performed once per year.

6 = For patient's entering the roll-over study, should complete an EOT visit within 4 months of the roll-over study being opened at the site.

7 = Not applicable to patients entering the roll-over study.

X=Assessments to be completed every 3 months for the first 18 months during Extension-2, and every 6 months until EOT Extension-2.

[redacted]

1 Introduction

1.1 Background

Cushing's syndrome (CS) is defined by chronic excess cortisol secretion, which results in a plethora of metabolic abnormalities leading to an increased cardiovascular risk and higher mortality rates than the normal population. The clinical symptoms of Cushing's syndrome include: obesity, insulin resistance, dyslipidaemia, severe fatigue and muscle weakness, hypertension, skin changes (striae, ulcers, hirsutism, acne), hypercoagulation, reduced immune response, CNS effects (depression, mood changes, and cognitive impairment), and menstrual disorders in women.

The most common cause of endogenous Cushing's syndrome is Cushing's disease, in which a pituitary tumor (usually benign) secretes excess adrenocorticotropic hormone (ACTH). The resulting increased levels of ACTH stimulate the adrenal glands to produce excess cortisol. Cushing's disease is a relatively rare (<10 cases/million people/year; prevalence of ~ 10-60 million), and most commonly affects adults aged 20-50, with a marked female preponderance.

The diagnosis of Cushing's disease is challenging, so patients often suffer for many years before receiving appropriate therapy. Diagnosis generally requires a 3 step process: (1) confirmation of hypercortisolemic state using 24 hour urine collections. Evening serum or saliva cortisol measurement and a low dose dexamethasone test may also aid in this confirmation; (2) identification of the source of excess cortisol (e.g. Cushing's disease, adrenal adenomas, carcinomas or hyperplasia, or an ectopic ACTH producing tumor) using plasma ACTH levels; (3) confirmation of a pituitary source of the elevated ACTH can be confirmed by either magnetic resonance imaging (MRI) or bilateral inferior petrosal sinus sampling (BIPSS) with a CRH stimulation test.

The primary treatment and standard of care for Cushing's disease is surgical removal of the pituitary tumor via transsphenoidal adenectomy. However, if the tumor is small or in a difficult location, resection can be challenging. Post-surgical remission rates of 70-80% have been reported, however long-term follow-up of patients in remission shows a significant incidence of recurrence - approximately 25% at 10 years (Bochicchio et al 1995, Sonino et al 1996). For patients whom surgery is not indicated or has not been successful, radiotherapy is a possible alternative; however, it is curative in only about 15-45% of patients. Thus, medical therapy, although not usually curative, is required for better control of excess cortisol levels in a substantial proportion of patients. A number of drugs are currently used off label for the treatment of patients with Cushing's disease, including metyrapone, ketoconazole, mitotane, and cabergoline. However, most elicit limited efficacy and work only in a minority (~ 30% or less) of patients mainly due to dose limiting toxicities of the drugs. Consequently, new medical therapies with improved safety profiles are a desirable alternate treatment for patients with Cushing's disease.

LCI699 is a potent inhibitor of 11β-hydroxylase, the enzyme that catalyzes the last step in the synthesis of cortisol. In this respect, it is similar to metyrapone, which is occasionally used to treat patients with Cushing's disease. Although metyrapone has an *in vitro* IC50 of ~7.5 nM against recombinant human CYP11B1 (i.e. 3 fold less than LCI699) it has a half-life of < 2

[redacted]

hours. As a result, doses of 1-2 g t.i.d of metyrapone are often needed for efficacy, and can cause significant gastrointestinal (nausea, vomiting, abdominal pain) and central nervous system (headache, dizziness and sedation/drowsiness) issues that limit patients tolerability to the drug.

Preliminary LCI699 data (as of Dec 2011) in Cushing's disease patients (baseline UFC range of 1.6-17.0xULN) from this proof of concept study demonstrated normalization of UFC on at least 1 assessment in 11 out of 11 subjects during the study. The primary endpoint was achieved by all 9 subjects who have completed the active treatment phase (10 weeks), 8 of whom had normal UFC levels on day 70. Geometric mean increase in plasma ACTH levels from baseline to week 10 was 2-3 fold. Increased ACTH levels could lead to the following undesirable effects: 1) Up regulation of 11B hydroxylase gene resulting in escape, 2) Overstimulation of adrenal androgen pathway resulting in virilization-related adverse events and 3) Accumulation of mineralocorticoid precursors resulting in hypokalemia, fluid retention and hypertension.

Amendment 4 will further explore the safety and efficacy of LCI699 in patients with Cushing's disease.

1.1.1 Relevant data summary

Preclinical toxicology studies up to 26-weeks in duration in the rat, and up to 39 -weeks in the dog have been completed. Clinical studies in healthy subjects (up to 2 weeks) and hypertensive patients (up to 8 weeks) have been conducted with LCI699. A summary of both preclinical and clinical findings are given below. A more detailed version of these results is available in the [LCI699 Investigator's Brochure].

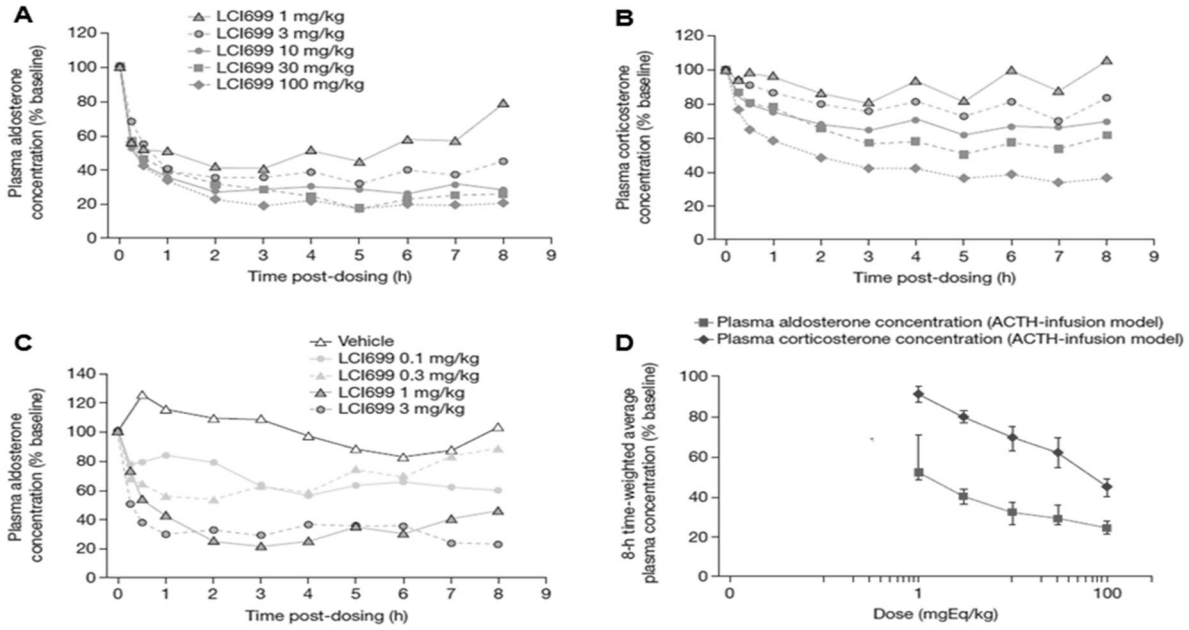
1.1.1.1 Preclinical data

LCI699 has been tested preclinically in a number of *in vivo* and *in vitro* mechanistic models. LCI699 inhibited recombinant human CYP11B1 (11β-hydroxylase; cortisol synthase) and aldosterone synthase (CYP11B2) *in vitro* in a dose-dependent manner (IC_{50} = 2.5 nM and 0.7 nM, respectively). In addition, LCI699 shows weak inhibitory activity towards human aromatase (IC_{50} = 1.7 µM); however, the enantiomer of LCI699, LCI698, is detectable at low levels in the drug product (<0.1%) and is a potent inhibitor of aromatase (IC_{50} = 9 nM).

The *in vivo* effects of LCI699 on inhibition of CYP11B1 and B2 were evaluated using a rat model where corticosterone and aldosterone synthesis were stimulated with a 9 hr ACTH infusion (Figure 1-1). LCI699 treatment resulted in a dose-dependent decrease in both corticosterone and aldosterone (ED_{50} = 73 and 1.1 mg/kg, respectively).

[redacted]

Figure 1-1 Effects of LCI699 on ACTH-stimulated cortisol and aldosterone synthesis in rats



Preclinical studies evaluated the safety pharmacology, general toxicity, and genotoxicity of LCI699 in rodents and dogs. No data of concern were obtained from *in vitro* or *in vivo* safety pharmacology studies including cardiac electrophysiology. No acute toxicity was observed in mice following administration of a single oral dose up to 125 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. The no observable adverse effect level (NOAEL) was 2 mg/kg in the rat (mean AUC of 5660 ng*hr/mL; estimated human equivalent dose of 50 mg bid based on exposure) based on liver findings in male rats, ovarian findings and clinical signs in females at a dose of 5 mg/kg/day in the 13-week rat study, and by liver findings in both sexes, adrenal gland and ovarian findings at doses of 20 mg/kg in the 26-week rat study. The NOAEL of 1 mg/kg in dogs (mean AUC of 659 ng*hr/mL; estimated human equivalent dose of 8 mg b.i.d. based on exposure) is based on clinical findings and adrenocortical changes at 10 mg/kg (mean AUC of 33750 ng*hr/mL) in the 13-week dog study.

Safety multiples for a 50 mg bid dose and 30 mg bid dose are summarized in Table 1-1.

[redacted]

Table 1-1 Safety multiples for 50 mg bid and 30 mg bid dose based on toxicology studies

Species (weeks of treatment)	Sex	NOAEL (mg/kg)	AUC_{0-24h} (ng.hr/mL)[a]	C_{max} (ng/ml)[a]	Exposure multiple for 50 mg bid [b]		Exposure multiple for 30 mg bid	
					AUC_{0-24h}	Cmax	AUC_{0-24h}	Cmax
Mouse	M	30	61500	14000	9.2	32.1	19.5	49.0
(13 wk)	F	30	52000	13300	7.7	30.5	16.5	46.5
Rat (4 wk)	M	5	17700	2670	2.6	6.1	5.6	9.3
	F	1	2290	581	0.3	1.3	0.7	2.0
(13 wk)	M	0.5	816	208	0.1	0.5	0.3	0.7
	F	0.5	726	232	0.1	0.5	0.2	0.8
(26 wk)	M	2	6170	869	0.9	2.0	2.0	3.0
	F	2	5150	931	0.8	2.1	1.6	3.3
Dog (4 wk)	M	10	39200	5640	5.8	12.9	12.4	19.7
	F	10	28300	6340	4.2	14.5	9.0	22.2
(13 wk)	M	1	713	372	0.1	0.9	0.2	1.3
	F	1	605	357	0.1	0.8	0.2	1.2
(39 wk)	M	10	22200	3770	3.3	8.6	7.0	13.2
	F	10	20300	3850	3.0	8.8	6.4	13.5

[a] Mean values obtained at end of dosing period from 13, 26 or 39 week oral studies
[b] Estimated human exposure data of mean AUC_{0-24h} (6716 ng.hr/mL) and Cmax (436 ng/ml) values at steady state after administration of 50 mg LCI699 bid
[c] Estimated human exposure data of mean AUC0-24h(3159 ng*h/mL) and Cmax (286 ng/mL) values at steady state after administration of 30 mg LCI699 bid

Reversible CNS effects were seen at very high doses in dogs (≥10 mg/kg; mean AUC of 33750 ng*hr/mL) and mice (doses ≥30 mg/kg; mean AUC of 56750 ng*hr/mL)). Hepatocellular hypertrophy (reversible) and vacuolation (partially reversible) were seen in 13 week and 26-week rat studies at doses ≥5 mg/kg (mean AUC of 17700 ng*hr/mL) and in a 13-week study in mice at doses ≥10 mg/kg (mean AUC of 8460 ng*hr/mL). Correlating increases (~2 -fold) in serum alanine aminotransferase activities were present in the mouse but not the rat. 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 rat female reproductive organs were present in the ovary (microscopic follicular degeneration at 4 weeks; prominent ovarian corpora lutea at 26-weeks), uterus (weight decrease and slight atrophy) of and vagina (mucification) 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 which were also reversible. Effects in rat female and male reproductive organs are consistent with effects seen after aromatase inhibition. No effects on female or male reproductive organs were found in dogs. In the adrenal cortex, morphological alterations were observed in dogs (zona glomerulosa; reversible) and at much higher exposure in rats (zona fasciculata/glomerulosa; partially reversible). They may be a result of the inhibition of adrenocortical steroid biosynthesis leading to an adaptive induction of the aldosterone/cortisol synthase pathway.

Estimated exposure multiples based on the NOAEL in repeated dose general toxicity studies and the estimated human exposure based on 50 mg twice daily dose are approximately 1 in

[redacted]

rats (based on NOAEL of 2 mg/kg) and 0.1 in dogs (based on NOAEL of 1 mg/kg) for AUC, and ≥ 2.0 and ≥ 0.9 for Cmax, respectively.

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.

1.1.1.2 Teratogenicity and reproductive toxicity data

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 (50 mg/kg; $AUC_{(0\text{-}24h)}$ =100000 ng*hr/mL) and the rabbit (10 mg/kg; $AUC_{0\text{-}24h}$=11800 ng*hr/mL). Safety margins at the no observed effect level (NOEL) are 0.1 in rat (0.5 mg/kg; $AUC_{0\text{-}24h}$=749 ng*hr/mL) and rabbit (3 mg/kg; $AUC_{0\text{-}24h=}$850 ng*hr/mL) EFD studies (AUC at NOEL vs. AUC at 50 mg b.i.d. in humans). LCI699 appears to be teratogenic in the rat at high doses that also produced maternal toxicity (50 mg/kg; $AUC_{0\text{-}24h}$=100000 ng*hr/mL). The safety margin at the NOEL for malformations (5 mg/kg; $AUC_{(0\text{-}24h)}$=12800 ng*hr/mL) is approximately 2 relative to a 50 mg b.i.d. dose. Reproductive performance in female rats was affected at 50 mg/kg (NOAEL=5 mg/kg; safety margin 1.7 relative to a 50 mg bid dose).

1.1.1.3 Human safety and tolerability data

LCI699 was studied in healthy male volunteers following administration of single doses up to 200 mg and following daily administration of up to 10 mg for 14 days. It was also evaluated in an ethnic sensitivity study of Caucasian and Japanese male healthy subjects. In addition, LCI699 has been studied in more than 500 patients with essential hypertension, resistant hypertension or primary hyperaldosteronism for up to 8 weeks of treatment, at doses ranging from 0.25 mg q.d. up to 1 mg bid.

Overall, LCI699 was well tolerated with the overall incidence of adverse events being similar to placebo. The most common AEs across all studies were headache, dizziness (including postural dizziness), nausea, diarrhea and fatigue. In general, these adverse events were not dose-related and most were mild to moderate in severity. Discontinuations due to an AE were infrequent, had no consistent pattern, and occurred at only a slightly higher rate with LCI699 treatment in comparison to placebo. Serious adverse events (SAEs) were infrequent and occurred at a rate similar to placebo. The incidence of hyperkalemia (>5.5 mmol/L was more common in the LCI699 and eplerenone groups in both the essential hypertension study (3-5% for active vs 0% for placebo) and the resistant hypertension study (5.6-6.1% for active vs 0% for placebo. In the study in patients with essential hypertension, there was a 20% incidence of an impaired ACTH-stimulated cortisol response (<500 nmol/L) with a daily dose of 0.5 mg b.i.d. or 1 mg q.d. LCI699, with no abnormal tests for lower doses of LCI699, eplerenone or placebo. There was no reduction in basal cortisol levels and there were no signs/symptoms of adrenal insufficiency observed across the dose range of LCI699 studied.

Preliminary data (as of Dec 2011) from this PoC study (n=11) showed that LCI699 was generally well tolerated; the most frequently reported adverse events were fatigue (5/11), nausea (4/11) and headache (3/11). Five of 11 subjects experienced ACTH levels >2 x baseline. Three of 11 subjects experienced study drug-related hypokalemia (K^+<3.5mmol/L; min 3.1 mmol/L). A tendency for decreases in mean systolic and diastolic blood pressure was

[redacted]

observed (mean change at day 70 was -13.1 and -9.3 mmHg for SBP and DBP respectively) although the sample size is too small to make an appropriate estimate of the effect.

There were no study drug related discontinuations, deaths or serious AEs of suspected drug relationship.

The dose at which patients had a normalization of UFC varied. Overall, all 11 patients had at least one UFC <ULN in recorded visits. One patient had normal UFC with a dose of 2 mg bid, 3 patients had normal UFC with a dose of 5 mg bid, 3 patients had normal UFC with a dose of 10 mg bid, one patient had normal UFC with a dose of 15 mg bid, two patients had normal UFC with a dose of 20 mg bid and one patient had a normal UFC with a dose of 50 mg bid.

LCI699 was generally well tolerated. There were no discontinuations due to adverse events or serious AEs of suspected drug relationship reported. Eleven patients reported at least one AE. Four patients experienced AEs consistent with cortisol withdrawal and they all improved upon dose reduction.

1.1.1.4 Human pharmacokinetic data

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. Tmax remained constant with increasing doses. Half-life was 3-5 hours across all doses examined. The pharmacokinetics of LCI699 displayed over-proportional increase in exposure with increasing dose over the 0.5 – 200 mg range. Consistent with its short half-life, LCI699 does not accumulate in plasma following multiple dosing at low doses, but is expected at 50 mg bid. Based on model-derived PK parameters, 50 mg b.i.d. is predicted to give a Cmax,ss of 436 ng/mL and AUC0-24hr,ss of 6716 ng.hr/mL at steady state. Additionally, based on the current proposed maximum clinical dose of 30 mg b.i.d, the predicted mean Cmax,ss and AUC0-24h,ss at 30 mg bid are 286 ng/mL and 3159 ng*h/mL at steady state, respectively.

Administration of 100 mg LCI699 with a high fat meal resulted in a reduction in both AUC and Cmax by 14% and 25%, respectively. The median Tmax was delayed from 1 hr to 2.5 hr after high fat meal. AUC was 47-68% higher in Japanese healthy volunteers in comparison to Caucasians (body weight difference was not a major determinant of race effect on exposure).

Formal drug-drug interaction studies have not been conducted with LCI699. However, based on *in vitro* CYP P450 inhibition profile (Ki values: CYP1A2 = 0.78 μM, CYP2D6 = 1.97 μM, CYP2E1 = 0.48 μM), steady state maximum concentrations at doses >20 mg b.i.d (e.g. 50 mg b.i.d: Cmax,ss = 436 ng/mL or 1.92 μM) and FDA regulatory guidance, LCI699 is likely to cause drug-drug interaction via inhibition of CYP1A2, CYP2D6 and CYP2E1 at these high doses.

Based on emerging preclinical data, CYP3A4/5 and CYP2D6 may be involved in LCI699 metabolism. The relative contributions of these enzymes on LCI699 metabolism is currently under investigation.

1.1.1.5 Human pharmacodynamic data

In healthy male volunteers ([CLCI699A2101]), LCI699 (0.5-200 mg once daily) reduced plasma and urine aldosterone levels. In response to inhibition of aldosterone, RAAS counter-

regulation was observed as evidenced by increases in plasma renin activity (PRA). After repeated once daily administrations, an increase in aldosterone above baseline values was evident upon termination of LCI699. LCI699 had no effect on basal (morning) cortisol after repeated doses of ≤ 3 mg, however, there was a significant dose- and time-dependent inhibition of ACTH-stimulated cortisol synthesis at doses ≥ 3 mg. Subsequent trials in healthy volunteers and patients with hypertension confirmed and refined these effects of LCI699 on the RAAS and hypothalamic-pituitary-adrenal-axis. In these trials, treatment with LCI699 caused a dose- and time-dependent inhibition of cortisol synthesis (ACTH-stimulated cortisol test), with the moderate inhibition at total daily doses 0.5 mg and increasing suppression to 10 mg (highest dose tested). As observed in healthy volunteers, basal morning cortisol concentrations were unaffected by LCI699 at these doses and no patients experienced the overt signs or symptoms of adrenal insufficiency. Full recovery of the ACTH-stimulated cortisol response was observed within a week after LCI699 was withdrawn.

The blood pressure lowering effects of LCI699 have been evaluated in four clinical trials. Treatment with LCI699 was associated with modest reductions in mean sitting systolic (MSSBP) and diastolic (MSDBP) blood pressure in patients with resistant hypertension and primary hyperaldosteronism. Greater reductions in MSSBP/MSDBP were observed in patients with essential hypertension. Despite its relatively short half-life, ambulatory BP monitoring indicated that the blood pressure lowering effects of LCI699 were sustained for 24 hours. No BP effects were observed in normotensive patients.

Preliminary data (as of Dec 2011) from this PoC study in Cushing's disease subjects (n=11) with a baseline UFC range of 1.6-17.0 x ULN showed that LCI699 normalized UFC on at least 1 assessment in 11 out of 11 subjects during the study. The primary endpoint was achieved by all 9 subjects who have completed the active treatment phase (10 weeks), 8 of whom had normal UFC levels on day 70. After treatment discontinuation, UFC was >ULN in 6 subjects with measurements at day 84. The median dose of LCI699 associated with UFC normalization was between 5 and 10mg bid. Geometric mean increase in plasma ACTH levels from baseline to week 10 was 2-3 fold. These data support further evaluation of LCI699 in Cushing's disease.

1.2 Study purpose

This exploratory study is designed as a proof of concept of LCI699 in patients with Cushing's disease. The purpose of this study is to determine whether the ability of LCI699 to inhibit 11β-hydroxlase can safely reduce urinary free cortisol (UFC) in patients with Cushing's disease. With the introduction of Amendment 4 this study aims to confirm the preliminary observations from this proof of concept (PoC) study by enrolling a new cohort (Expansion cohort) of patients and evaluating the long-term efficacy and safety of LCI699 treatment for a total duration of 22 weeks. This longer treatment period will help address questions on the sustainability of the cortisol reductions and potential longer term safety issues (e.g. increases in ACTH levels and off-target effects on the mineralocorticoid and androgen pathways).

With Amendment 4, approximately 15 new patients (not previously enrolled) with Cushing disease will be enrolled as the Expansion Cohort. Patients who previously completed the trial prior to Amendment 4 and benefited from the treatment with LCI699 will also be allowed to re-enter the study as the Core PoC Follow-up Cohort. These patients will start the study over

[redacted]

again at screening and follow through the visit schedule the same as new patients with certain differences described in Section 3.1. Core PoC Follow-up patients can reenter if their UFC is > ULN and all other eligibility criteria have been met.

2 Study objectives

2.1 Primary objective(s)

- To assess the effect of 10 week treatment LCI699 on 24 hour urine free cortisol (UFC) in patients with Cushing's disease.

2.2 Secondary objective(s)

- To assess the 10 week safety and tolerability of multiple doses of LCI699 in patients with Cushing's disease.
- To assess the 22 week safety and tolerability of multiple doses of LCI699 in patients with Cushing's disease.
- To assess the effect of LCI699 on steroid hormones of the HPA-axis in plasma, urine and saliva.
- To assess the effects of LCI699 on improving the metabolic abnormalities (hypertension, dyslipidaemia, obesity, insulin sensitivity, HbA1c and FPG) of Cushing's disease.
- To assess the steady state pharmacokinetics of LCI699 in patients with Cushing's disease.
- To assess the effect of 22 weeks of treatment with LCI699 monotherapy on 24 hour urine free cortisol (UFC) in patients with Cushing's disease. The proportion of patients with controlled or partially controlled will be determined as follows:
  - Controlled UFC: defined as a mean UFC level ≤ ULN.
  - Partially controlled UFC: defined as a mean UFC level > ULN but with ≥ 50% reduction from baseline.
- To assess escape Escape is defined as loss of UFC control (i.e. UFC > ULN) on at least 2 consecutive visits at the highest tolerated dose after previously attaining UFC normalization.

3 Investigational plan

3.1 Study design

This is a proof of concept, open-label, single arm, sequential dose-escalation, multi-center study to assess the safety/tolerability and efficacy of 10-weeks treatment of LCI699 followed by a 12-week treatment period in patients with Cushing's disease.

The study will consist of a screening period of up to 60 days (to allow an adequate washout period for any medications that modify cortisol levels), a 10-14-day baseline period, a 10-week sequential dose escalation treatment period, a 12-week treatment period on the last efficacious dose, an End of Treatment-Core evaluation and two optional extensions. Patients are to have an end of study (EOS) visit 28 days after the last drug administration.

With Amendment 4, approximately 15 new patients (not previously enrolled) with Cushing disease will be enrolled as the expansion cohort. Patients who previously completed the trial prior to Amendment 4 and benefited from the treatment with LCI699 will also be allowed to re-enter the study as the core PoC follow-up cohort. These patients will start the study over again at screening and follow through the visit schedule the same as new patients with certain differences described below. Core PoC follow-up patients can reenter if their UFC is > ULN and all other eligibility criteria have been met.

Screening and baseline period:

Patients who meet the eligibility criteria at screening and are either not on medications that effect cortisol levels or have completed the required washout period of these medications, will proceed to baseline evaluations. Patients will be instructed in the proper method for collecting 24 hour urine and saliva. Every 7 days during the baseline period, patients will collect a morning and evening saliva sample (upon waking and just prior to bedtime e.g. 6-8:00 and 23-24:00, respectively). In addition, the patient will perform at least three 24 hour urine collections. Patients will bring in their urine collection bottles on Day -7. At this time, baseline safety and PD samples will be collected. All baseline evaluation results must be reviewed, and confirmation of inclusion/exclusion criteria determined prior to the patient starting dosing with LCI699. Patients will receive medication for the next 2 weeks on Day 1.

Dose escalation period:

Patients that meet all inclusion/exclusion criteria at baseline will begin taking their first dose of LCI699 the morning of Day 1. Due to the circadian rhythm nature of steroid levels (including cortisol), patients are advised to come to the clinic on a fixed time window (such as ± 2 hrs) for each of the visit and best efforts should be made to keep consistent throughout the study.

Expansion cohort:

Patients will continue to take their prescribed medication every morning and evening. Patients with a baseline UFC ≤ 3 x ULN will start at 2 mg bid on Day 1. Patients with baseline UFC > 3xULN will start at 5 mg bid on Day 1. On Day 7, the patient will be contacted by the site staff to ensure patients are taking their study medication and to record any adverse events.

[redacted]

Every 7 days during the dose escalation period, patients will collect a morning and evening saliva sample (upon waking and just prior to bedtime e.g. 6-8:00 and 23-24:00, respectively). Patients will perform three 24 hour urine collections within 4 days of Day 14 ± 2 days. Patients will report to the site in a fasted state, the morning of Day 14 ± 2 days with their urine collection. A predose PK sample (12 hr post previous PM dose) will be collected and post-dose PK samples at 1, 1.5, 2, 4, and 6 hours post morning dose will be collected. A meal will be provided 4 hours after the AM dose. Patients will undergo safety/PD assessments and be sent home with medication for the next 2 weeks, with instructions to wait for confirmation of the dose to be taken pending the UFC results.

If UFC > ULN, the site will contact the patient to plan an interim escalation dose visit 7 days after the regular visit (on Day 21). At the interim visit, the patient will take the first escalated dose at the site, and remain for 1.5 hours in order to have a 12-lead Safety ECG. This ECG must be read on site by a qualified physician (e.g., the investigator, or another qualified physician such as a consulting cardiologist), who will decide whether or not there is a "notable abnormality". Notable abnormality is defined as QTcF > 480msec with acute cardiac risk, QTcF > 500msec, or increase in QTcF > 60msec from baseline QTcF from the pre-dose ECG taken on the day of the first study drug administration (Day 1). If there is no notable abnormality, then the patient will be sent home to continue the higher dose until the next visit on the current schedule. 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.

This schedule of events will continue every 2 weeks (i.e. Day 28, 42, 56) with potential interim dose escalation visits (on Days 35, 49, 63) during the dose escalation period, with the dose of LCI699 increasing according to Figure 3-1. If at any time, the patients UFC is < ULN, dose escalation will be halted and the patient will remain on the current, efficacious dose through the rest of the dose escalation period (Week 10), and if UFC remains normal, continue until Week 22. Monitoring of UFC responses will continue every 2 weeks to allow additional dose adjustments if necessary. Accordingly, only a predose PK sample will be required for patients that remain on the efficacious dose. If at any time the patient experiences side effects which are either intolerable or meet dose adjustment criteria, the prescribed dose will be adjusted as outlined in Section 5.5.4.

Between days 66-69, patients will perform three 24-hour urine collections. Patients will bring in their urine collection bottles to the site on Day 70 ± 2 days. A pre-dose PK sample only (12 hr post previous PM dose) will be collected for patients on their previous maintained dose (<30 mg bid). Pre-dose (12 hr post previous PM dose), 1, 1.5, 2, 4 and 6 hour PK samples will be collected for patients receiving 30 mg bid. Patients will undergo safety/PD assessments at the site on Day 70 ± 2 days.

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

Core PoC follow-up cohort:

Patients who previously completed the study prior to Amendment 4 and reenter the study will be started at the penultimate LCI699 dose that was efficacious and well tolerated with the

[redacted]

possibility to up-titrate the dose within one week based on tolerability. Patients should be sent home with enough medication to allow for up titration on Day 7 with instructions to wait for confirmation of the dose to be taken pending tolerability as assessed by the Investigator. Additional dose titrations will be done as needed based on efficacy and tolerability. They are to complete all assessments during that phase as indicated in the Assessment Schedules. The 6-hr PK profile blood samples (predose, 1, 1.5, 2, 4, and 6 hr post dose) will only be collected from these patients at day 14, and only pre-dose PK blood samples will be collected in the following visits.

12 -week assessment period:

At Day 70 ± 2 days (Week 10), all patients (both patients entering for the first time and those re-entering the study) will enter the 12 week assessment period. Three visits will be performed at Day 98, Day 126 and Day 154. Patients will continue the home saliva collections every 7 days twice daily (upon waking and just prior to bedtime e.g. 6-8:00 and 23-24:00 respectively). Patients will perform three - 24 hour urine collections over 7 days prior to the next scheduled visit. Patients will report to the site in a fasted state, the morning of scheduled visits with their urine collections and undergo safety/PD assessments. In addition, a predose PK sample will be collected during their visits.

From Day 70 through Day 154, patients can have the LCI699 dose adjusted based on the criteria in Section 5.5.4). At Day 154, patients will complete the End of Treatment-Core visit. Patients not continuing into the optional long term extension-1 will also complete an End of Study visit 28 days after the last dose administration.

Optional long term extension-1

At Day 154, patients have the option to enter the 12 month extension phase at the investigators discretion provided they do not meet any discontinuation criteria. Dosing titration during the extension is to be based on efficacy (UFC control) and safety (Section 5.5.4). Patients will come in for monthly visits for the first 6 months (Day 154- Day 322) of the long-term extension and then will have visits every 3 months from month 6 through 12 (Day 322 - Day 490). At the end of the extension phase, patients will complete and End of Treatment-Extension visit at Day 490 and an End of Study visit 28 days after the last dose administration, if not continuing into long term Extension-2.

Optional long term extension-2

At Day 490, patients have the option to enter a second long term extension phase (extension-2) at the investigator's discretion, provided they do not meet any of the study discontinuation criteria. Dose adjustment during the extension is to be based on efficacy (UFC control) and safety (Section 5.5.4). Patients will come in for visits every 3 months during the first 18 months of extension-2 (approximately 3 years into the study), and every 6 months thereafter. This additional long term extension (extension-2) will provide important long term safety and efficacy data of LCI699 in patients with Cushing's disease.

1. Patient treatment in Long Term Extension-2 will end at each site within 4 months after a separate roll-over study is opened at their site, or by 31 December 2019 (whichever occurs

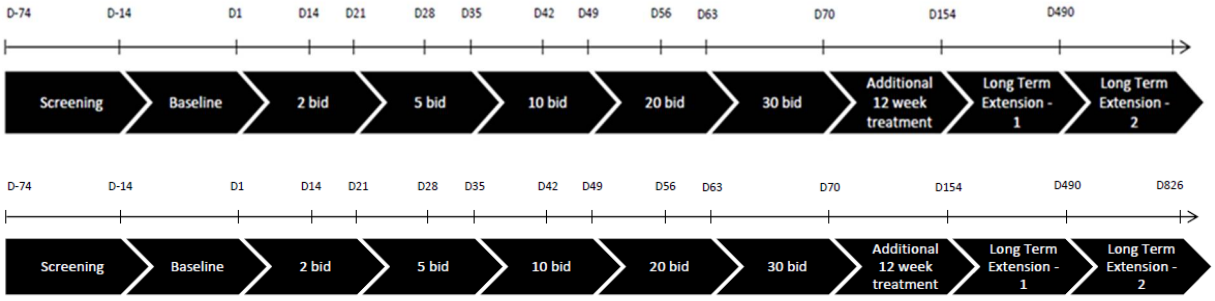
[redacted]

earlier). The roll-over study will provide an opportunity of continued treatment for patients who are still ongoing at that time and who are clinically benefitting from LCI699. For sites where a separate roll-over study is not an option, the patient may be offered a local alternative treatment option.

Patients entering the roll-over protocol will complete an EOT visit. For these patients the EOS visit is not applicable, as treatment on LCI699 will not be interrupted. Sites with the separate roll-over study option available, should arrange their patient's End of Treatment (EOT) visit within 4 months of the roll-over study being opened at their site (i.e. earlier than the 6 month visit intervals in Long-Term Extension-2), to allow their patients to continue their LCI699 dose on this new study.

Patients not continuing into the roll-over protocol will complete an EOT visit upon stopping treatment, and an EOS visit 28 days after the last dose administration, must be completed by 31 December 2019.

Figure 3-1 Study design



*Note: Patients with baseline UFC > 3xULN will start at 5 mg bid (in lieu of 2 mg bid) at Day 1

3.2 Rationale of study design

The design of this study addresses the primary objective of reduction of UFC in patients with Cushing's disease, and takes into account the rarity of this disease and the objective nature of the measurement. A dose titration design was chosen for this proof-of-concept study because it provides a fast yet reasonable first approximation of dose-response, and allows individualization of therapy for this disease. Cushing's disease patients are scarce and compared to a parallel dose-response study, this design uses fewer patients, yet allows the testing of multiple doses. In addition, as the level of cortisol can be extremely varied in patients with Cushing's disease due to tumor size and degree of compensatory mechanisms, dose titration to efficacy will reduce unwanted side effects and also reflects clinical practice for the treatment of this disease. While such a design inherently shows that higher doses are the most effective, especially if the pharmacodynamic response is time-dependent, this design can provide valuable data to aide dose selection for a subsequent parallel dose-response study. Given the objective nature of the UFC measurement, an open-label, non-comparator design was chosen to further reduce patient numbers in this proof of concept study. Twenty-four hour UFC measurements were chosen for the primary outcome measure of the study as it is a well-accepted measure of disease activity and allows for the circadian variability and pulsatile

nature of ACTH secretion in patients with Cushing's disease. The mean of 3 UFC measurements will be used to account for the intra-patient variability in the 24-hour UFC measurement in patients with Cushing's disease.

Amendment 4 introduces an additional 12 week treatment period following the 10 week dose-escalation phase. The aim of Amendment 4 is to confirm the preliminary observations from the proof of concept evaluation and evaluate the long term efficacy and safety of LCI699 in patients with Cushing's disease. In particular, this extended treatment with LCI699 will help address questions on the sustainability of cortisol reductions (or escape) and the effect of LCI699 therapy on steroid hormones of the HPA-axis and metabolic effects. Two consecutive, optional long-term extensions (extension-1 and extension-2) will further establish the safety and efficacy profile of LCI699 in patients with Cushing disease.

3.3 Rationale of dose/regimen, duration of treatment

Treatment duration of 10 weeks was chosen to allow for multiple dose escalations, if required, and to allow possible rebound or break through of the inhibition to be examined. The inhibition of cortisol synthesis by LCI699 also appears to be time-dependent. Data to-date suggests that the maximal inhibition occurs by 2-4 weeks of treatment. Given this dose escalation every 2 weeks was chosen. Amendment 4 extends the evaluation of LCI699 for a total of 22 weeks in order to assess the sustainability of the cortisol reductions over time as well as potential off -target effects affecting the mineralocorticoid and androgen pathways and any effects on corticotroph tumor volume. The half-life of LCI699 is 4-5 hour and therapy will therefore be administered b.i.d. in this study. The two consecutive optional long term extensions (extension-1 and extension-2) have been added to generate further efficacy and safety data.

Inhibition of cortisol synthesis with LCI699 is dose-dependent. Looking across the 6 studies performed in patients with "normal" cortisol levels, a notable inhibition of cortisol synthesis (based on an ACTH-stimulation test) was at ~2 mg/day (2 mg qd or 1 mg bid) after 2-4 weeks of treatment. No notable change in basal (morning) cortisol levels were observed at these doses (likely due to the compensatory rise in ACTH to maintain the cortisol levels), but reduction in 24-hour urinary cortisol has been observed at 1 mg bid in patients with primary aldosteronism.

Based on modeling of PK and PD data, a dose of 4-5 mg bid is expected to achieve a plasma concentration above the IC50 for CYP11B1 (2.5 nM) for a full 24 hours. As the current study represents the first time LCI699 will be administered to patients with elevated levels of cortisol, a dose of 2 mg bid was chosen as the starting dose. This dose will transiently achieve plasma concentration above the IC50, but not for the full 24 hours and therefore, this dose is expected to be minimally effective at reducing UFC in these patients and have few side effects. Preliminary results from this study are consistent with the PK/PD simulations in that the starting 2 mg BID dose was a fully efficacious dose for only 1 of 12 patients. In view of the need to obtain more rapid control in patients with severe hypercortisolism patients with baseline mUFC > 3xULN will not undergo the initial 2-week treatment with LCI699 2 mg bid, and will instead be started on the 5 mg bid dose.

[redacted]

Based on repeated dose toxicology studies, the NOAEL in rat has been set at 2 mg/kg (mean AUC of 5660 ng*hr/mL) based on the 26-week study. While lower NOAEL were identified in shorter term studies, in all cases, the NOAEL was determined based on reversible adverse effect observed at doses ≥5 mg/kg (Table 3-1). In the dog, the NOAEL has been set at 1 mg/kg (mean AUC of 659 ng*hr/mL) based on the 13-week study where reversible clinical signs of aggression were observed in 1 female at 10 mg/kg in this study. In both the 4- and 39-week studies, the NOAEL was 10 mg/kg (mean AUC of 21250 ng*hr/mL for 39-wk study). Based on these data, we had originally planned to escalate to a maximum of 50 mg bid in this study.

However, at the time of protocol Amendment 5, on the basis of preliminary clinical data showing a potential risk of QTc prolongation, the maximum dose has been reduced to 30 mg bid. The rationale for this change is that the results of the exploratory post-hoc analysis of QTcF in relation to LCI699 dose from the phase-I study [LCI699A2101] found no evidence of a QTcF prolongation effect after a single 30 mg dose, but did find substantial QTcF changes (some patients with QTcF prolongation > 30ms) at single doses of 100 mg and 200 mg. Since it is not yet clear at which dose or plasma concentration of LCI699 the threshold for a QT prolongation effect is, the 50 mg bid dose was removed as a precaution.

The exposure at the 30 mg bid dose is estimated to be: Cmax = 286 ng/mL and AUC0-24= 3159 ng*h/mL. Based on the NOAEL exposures in long term rat (26 week) and dog (39 week) studies safety margins would be ~ 1.6 – 7 at the 30 mg bid dose (see Table 1-1). Since the NOAEL defining toxicities (Table 3-1) were either monitorable and/or reversible, the ability to slowly dose escalate to the preclinical NOAEL is warranted in this proof-of-concept study.

Table 3-1 NOAEL determining toxicology

Species	Dose	NOAEL effects
Rat	2 mg/kg	Reversible adverse effects: female reproductive tract atrophy changes, liver hypertrophy and vacuolation, and adrenal cortex hypertrophy/vacuolation of the zona fasciculata at doses >/= 5 mg/kg
Dog	1 mg/kg	Clinical signs of aggression in one female at 10 mg/kg in the 13-week study, not seen in the 39 week study. This effect is clinically monitorable.
Mouse	30 mg/kg	No adverse effects at 30 mg/kg. Doses between 30 and 100 mg/kg have not been evaluated

3.4 Rationale for choice of comparator

Not applicable.

3.5 Risk/ benefit for this study

Potential benefits

Biochemical remission is a goal in the treatment of Cushing's disease. Preliminary data from this PoC study in patients with Cushing's disease clearly demonstrated that LCI699 can reduce and normalize plasma cortisol in this population. However, it is unknown whether patients responding to LCI699 will eventually loose UFC control. Patients will be discontinued from LCI699 treatment in case of unsatisfactory response.

[redacted]

The primary treatment and standard of care for Cushing's disease is surgical removal of the pituitary tumor via transsphenoidal adenectomy. Therefore, in order to avoid any potential delay in receiving first line treatment patients enrolled under Amendment 4 should have either failed standard therapy (including surgery) or can be de novo patients for whom surgery is not an option. Given LCI699's potency to suppress cortisol synthesis, it is conceivable that patients may ameliorate some of the sequelae of their hypercortisolism state while on the drug for the planned duration of this study protocol following Amendment 4. Patients who are responding to LCI699 with good tolerability have the option to participate in optional two long term extension phases of the study.

Potential risks

Based on the preclinical and clinical experience with LCI699 the risks associated with this study are outlined below. The risks to patients will be minimized by strict inclusion/exclusion criteria, close clinical monitoring and predefined dose adjustment and dose termination criteria (see Section 5.5.4 and Section 5.5.9).

Effects on QTc interval

Final results from the completed ICH E14-compliant thorough QT Study LCI699C2105 showed that the predicted mean QT effect of osilodrostat was below the threshold of regulatory concern for the currently investigated dose range (2-30 mg twice a day [bid]).

Effects on blood pressure

LCI699 has been shown to reduce BP of hypertensive patients in a dose dependent manner over 4-8 weeks. An acute decrease in BP has not been observed with LCI699 in healthy volunteers (up to 200 mg) or hypertensive patients (range tested = 0.25 mg - 2 mg/day). Doses used in this study will be higher than those where a BP effect was observed, and may therefore elicit larger decreases in BP than observed to-date. Patients with Cushing's disease have a high prevalence of hypertension and effective treatment of hypercortisolism may result in reductions in blood pressure.

In the studies performed to-date, an increase in the precursor to aldosterone, 11-deoxycorticosterone (DOC) has been observed. DOC is also a potent mineralocorticoid which may replace aldosterone on its receptor. The levels of DOC were further increased at doses that inhibited cortisol, presumably driven by the rise in ACTH. In patients with already elevated levels of ACTH, combination with aldosterone blockade may lead to high levels of 11-DOC which could increase BP, decrease potassium, and cause fluid retention.

Preliminary data from this PoC study in CD patients (using doses higher than those tested in the hypertension studies) showed a tendency for decreases in mean systolic and diastolic blood pressure although the sample size is too small to make an appropriate estimate of the effect. During the extended treatment period introduced by Amendment 4, patients will be re-educated on signs and symptoms of hypotension/ hypertension and BP will be monitored throughout the study.

[redacted]

Effects on the serum electrolytes

Blockade of aldosterone may physiologically increase potassium levels (hyperkalemia) and reduce sodium levels (hyponatremia). While reports of these abnormal laboratory parameters have generally been infrequent, transient, and mild in the studies conducted to-date with LCI699, serum electrolytes will be monitored closely. In addition, inclusion/exclusion criteria for baseline sodium and potassium levels will be strictly enforced.

Furthermore, levels of DOC might further increase at doses of LCI699 that inhibit cortisol, presumably driven by the rise in ACTH. In patients with already elevated levels of ACTH (i.e. Cushing's disease) combination with aldosterone blockade may lead to high levels of DOC which could lower blood potassium.

Preliminary data from the PoC study in Cushing's disease patients showed the following out of range potassium levels: 3 subjects had potassium levels < 3.5 mmol/L whereas 2 subjects had potassium levels > 5.3 mmol/L. Minimal or no changes were observed in plasma sodium.

Serum electrolytes will continue to be closely monitored during the extended study protocol.

Effects on adrenal hormones

Inhibition of both cortisol and aldosterone has the potential of rendering a patient adrenally insufficient. Patients will be provided with an instruction sheet surrounding adrenal insufficiency and details of rescue medications that can be taken. Clinical sign/symptoms of this condition include chronic fatigue, muscle weakness, nausea, vomiting, hypotension and hypoglycemia. Symptoms of frank adrenal insufficiency have not been observed to-date with LCI699 however symptoms suggestive of cortisol withdrawal were reported by 4 patients in the PoC study which were easily managed by dose adjustments of LCI699 with minimal clinical sequelae. Blood chemistry and clinical vital sign assessments will be reviewed every 2 weeks for the first 10 weeks, monthly thereafter and as clinically needed. In addition, reported adverse events will be monitored.

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.

Effects of sex hormones

General toxicology and reprotoxicology studies in rats/rabbits have identified reproductive organs (ovaries, uterus, vagina and prostate) as target organs of toxicity for LCI699 (Table 3-2). These reversible findings may be attributed to off target effects of LCI699 to inhibit aromatase (enzyme that converts testosterone to estradiol and andstenedione to estrone). LCI699 has weak *in vitro* inhibition of human aromatase (IC_{50} = 1.7 µM), and the drug's

[redacted]

enantiomer (LCI698; present at approximately 0.06% in the clinical batch) has considerably higher aromatase inhibitory activity (IC_{50} = 9 nM). Based on the predicted Cmax of 0.8µM (free drug) in human at the dose of 30 mg b.i.d., aromatase inhibition may be of relevance in humans at the exposures to be achieved in this study.

In addition, inhibition of aldosterone and cortisol can lead to build up of precursors. As some of the early precursors in the synthesis pathways are also common to sex steroid synthesis (e.g. pregnenolone and 17-OH pregnenolone) and therefore could lead to increased synthesis of sex steroids, like testosterone and estradiol. Since patients with Cushing's disease are typically hypogonadal, the increase in sex steroid levels may place them within the normal reference range. However, the magnitude of increase in sex steroids will need to be observed long-term to evaluate whether the levels become elevated above the normal range. Hirsutism and acne may result from increased androgen levels in female patients. These effects would be expected to reverse when the drug is withdrawn.

For these reasons, females that participate in the study will be asked to refrain from getting pregnant for the duration of the study. In addition, they must agree to use 2 forms of birth control. Furthermore, testosterone and estradiol levels will be measured every 2 weeks for the first 10 weeks and monthly thereafter.

Table 3-2 Safety multiple for 50 mg bid dose based on reprotoxicity studies

Study	Generation or gender	NOAEL (mg/kg)	AUC0-24h (ng.hr/mL)[b]	Cmax (ng/ml)[b]	Exposure multiple [a]	
					AUC0-24h	Cmax
EFD rabbit	Maternal	3	850	481	0.1	1.1
	Fetal	3	850	481	0.1	1.1
EFD rat	Maternal	0.5	749	172	0.1	0.4
	Fetal	5	12800	1920	1.9	4.4
FEED rat	Males	50	1E+05	11400	14.9	26.1
	Females	5	11400	2260	1.7	5.2

[a] Estimated human exposure: AUC0-24h = 6716 ng.hr/mL, Cmax = 436 ng/ml at steady state after 50 mg bid LCI699
[b] measured in maternal blood, except for FEED study where values from 13-week study day 75 are used

In addition, due to the potential androgenic effect of LCI699 (and atherogenic lipid changes), a full lipid profile has been added to each visit as part of Amendment 4 and will include TC, TG, HDL-cholesterol and LDL-cholesterol.

Potential impact of discontinuing therapy

Some patients who enter this study may wash out current drug therapies in order to participate in this trial. It is to be expected that patients willing to consider washout of current therapies are those who are not responding to or tolerating their current therapies, and for whom the risk of a relatively short washout may be considered acceptable to test whether another therapy works better. There is a theoretical risk that if current effective therapy would be withdrawn, that cortisol levels would increase, and that patients would not respond well to LCI699. However, preliminary data from this PoC study indicate that all patients analyzed responded to LCI699. There is a risk that some patients may lose UFC control over time ("therapeutic escape") while participating in the longer treatment evaluation. If a patient is not responding

[redacted]

to, or not tolerating an effective dose of, LCI699, they can be withdrawn from the study and resume their prior therapy.

Potential impact of delaying therapy

Some patients who enter this study may have a new diagnosis of Cushing's disease. The standard of care therapy for Cushing's disease is surgical resection of the ACTH producing tumor.

Entry into this study may delay the time to the provision of standard effective therapy. If LCI699 is effective, initiation of medical therapy to reduce excess cortisol may improve patient symptoms and improve medical co-morbidities which can improve their ability to tolerate the surgery. If LCI699 is not effective, the patient may experience extra weeks of excess cortisol exposure. If a patient is not responding to, or not tolerating an effective dose of, LCI699 they can be withdrawn from the study and undergo surgical resection.

The standard of care therapy for Cushing's disease is surgical resection of the ACTH producing tumor. Cushing's disease patients enrolled under Amendment 4 should have either failed standard therapy (including surgery) or can be de novo patients for whom surgery is not an option.

Preliminary data from this PoC study demonstrated that LCI699 is an effective medical therapy to reduce hypercortisolism. If a patient is not responding to, or not tolerating an effective dose of, LCI699 they can be withdrawn from the study (Section 5.5.9).

3.6 Purpose and timing of interim analyses/design adaptations

Because this is an open label study, response to the therapy will be monitored as the study proceeds. In addition, an interim analysis will be performed after the first 12 patients complete 10 weeks of treatment and a CSR will be generated from this data. Additional interim analyses may be conducted for the expansion cohort and the core-PoC follow-up cohort.

4 Population

The study population will be comprised of male and female patients with endogenous hypercortisolism due to increased ACTH production from the pituitary (Cushing's disease). Approximately 15 patients (not previously enrolled in the trial) with Cushing's disease will be enrolled to participate in the study (expansion cohort). At least 8 patients are expected to complete the study. Patients who previously completed the trial prior to Amendment 4 and benefited from the treatment with LCI699 will also be allowed to re-enter the study (core PoC follow-up cohort). These patients will start the study over again at screening.

The investigator must ensure that all patients being considered for the study meet the following eligibility criteria. No additional exclusions should be applied by the investigator, in order that the study population will be representative of all eligible patients.

Patient selection is to be established by checking through all inclusion/exclusion criteria at screening and study baseline. A relevant record (e.g. checklist) must be stored with the source documentation at the study site.

Deviation from **any** entry criterion excludes a patient from enrollment into the study.

4.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill **all** of the following criteria at the screening or baseline visit as described in the Assessment Schedules:

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:
   - UFC >1.5XULN (Mean value of three 24-hour urine samples collected within 14 days) [For Patients who completed the first 10 weeks of treatment prior to Amendment 4 (Core PoC follow-up cohort), the appropriate washout of medical treatment for Cushing's disease has to be followed per inclusion criteria 5. These patients must have UFC >1 X ULN (Mean value of three 24-hour urine samples collected within 14 days).]
   - Morning plasma ACTH above lower limit of normal
   - Confirmation of pituitary origin of excess ACTH by at least one of the following three:
     1. History of MRI confirmation of pituitary adenoma (greater than or equal to 6 mm) with positive dynamic test (e.g. CRH or high dose dexamethasone suppression test)

   or

     2. History of inferior petrosal sinus sampling in patients with a tumor less than 6 mm that meet any of the following criteria with either CRH or DDAVP (desmopressin) stimulation:
        - Central to peripheral ACTH ratio ≥ 2 at pre-stimulation baseline, or
        - Central to peripheral ACTH ratio ≥ 3 after CRH stimulation.

   or

     3. Prior pituitary surgery with histopathology confirming an ACTH staining adenoma
        - Patients are permitted to washout current drug therapy to meet these entry criteria if they have a known diagnosis of Cushing's disease
4. Patients with de novo Cushing's disease can be included only if they are not considered candidate for surgery (e.g. poor surgical candidates, surgically unapproachable tumors, patients who refuse to have surgical treatment or surgical treatment is not available)
5. For patients on medical treatment for Cushing's disease the following washout periods must be completed before baseline efficacy assessments are performed
   - Inhibitors of steroidogenesis (ketoconazole, metyrapone): 1 week
   - Dopamine agonists (bromocriptine, cabergoline), PPAR-gamma agonists (rosiglitazone, pioglitazone): 4 weeks
   - Octreotide LAR, Pasireotide LAR and Lanreotide autogel: 8 weeks
   - Mifepristone, Lanreotide SR: 4 weeks
   - Octreotide and Pasireotide (immediate release formulation): 1 week
   - Other experimental therapy: at least 5 half-lives

[redacted]

4.2 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 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 any of the study drugs 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. Pregnant or nursing (lactating) women.
5. 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:**
   - 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.
   - 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 oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
   - 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.
   - 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,
     d. In case of use of oral contraception women should have been stabile on the same pill for a minimum of 3 months before taking study treatment.
6. Fertile males, defined as all males physiologically capable of conceiving offspring UNLESS they use a condom during intercourse while taking the study medication and for 1 week after stopping study medication and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.
7. Patients who have been treated with mitotane during the last 6 months prior to Visit 1.
8. Patients with compression of the optic chiasm, in order to exclude patients with a tumor causing chiasmal compression requiring surgery.

[redacted]

9. Patients who have a known inherited syndrome as the cause for hormone over secretion (i.e. Carney Complex, McCune-Albright syndrome, MEN-1, AIP).
10. Patients with Cushing's syndrome due to ectopic ACTH secretion or adrenal Cushing's syndrome.
11. Patients with pseudo-Cushing's syndrome (for patients with a mean UFC < 3xULN further testing to rule out this condition will be required unless Cushing's disease is confirmed by histopathology.) At least 2 of 3 tests should be abnormal in order to exclude pseudo-Cushing's: low-dose dexamethasone suppression test, dexamethasone-CRH test or late salivary or serum cortisol.
12. Patients with renal impairment (estimated creatinine clearance < 60 ml/min by the MDRD formula), serum creatinine >2.0 X ULN.
13. Patients who are not biochemically euthyroid.
14. Patients who have undergone major surgery within 1 month prior to screening.
15. Diabetic patients with poorly controlled diabetes as evidenced by $HbA1_c$ > 9 %.
16. Patients who have congestive heart failure (NYHA Class III or IV), unstable angina, sustained ventricular tachycardia, clinically significant bradycardia, advanced heart block, history of acute MI less than one year prior to study entry or clinically significant impairment in cardiovascular function.
17. Patients with liver disease such as cirrhosis, chronic active hepatitis, or chronic persistent hepatitis, or patients with ALT/AST more than 3 X ULN, serum bilirubin >2.0 X ULN.
18. 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.
19. Patients who have a history of alcohol or drug abuse in the 6 month period prior to treatment.
20. 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.
21. Patients who have received pituitary irradiation within five years prior to Visit 1.
22. Patients with risk factors for QTc prolongation or Torsade de Pointes, i.e. patients with a baseline QTcF > 470ms, hypokalemia, hyperkalemia, hypocalcaemia, hypomagnesaemia, uncontrolled hypothyroidism, personal or family history of long QT syndrome, or concomitant medications known to prolong the QT interval.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

5 Treatment

5.1 Investigational treatment

The investigational drug, LCI699 1 mg and 5 mg capsules, will be prepared by Novartis and supplied to the Investigator as open labeled bulk medication.

In addition, LCI699 open labeled 1mg, 5mg, 10mg and 20mg tablets will be prepared by Novartis and supplied to the Investigator.

[redacted]

5.2 Treatment arms

This study has only one treatment arm; LCI699. Patients will start on a dose of 2 mg b.i.d. if baseline mUFC is ≤ 3x ULN or 5 mg b.i.d. if baseline mUFC is > 3x ULN and increase their dose every 2 weeks as illustrated in Figure 3-1 up until week 10. From week 10 to week 22, the dose will be adjusted as needed based on efficacy and tolerability.

5.3 Treatment assignment

Treatment numbers will be assigned in ascending, sequential order to eligible patients in accordance with entry into the study. The treatment number becomes the definitive subject number as soon as a patient receives the first dose of the respective study treatment.

5.4 Treatment blinding

Not applicable as this study is open label.

5.5 Treating the patient

5.5.1 Patient numbering

Screening number

Each patient screened is assigned a unique screening number. The screening number is a combination of the center number, which is provided by Novartis, and a three digit number starting with [redacted] for each patient which is assigned by the Investigator. Therefore, if the center number is [redacted] (any leading zeros in the center number are dropped) the screening numbers will be assigned such as [redacted] in ascending order. If the center number is [redacted] the screening numbers will be [redacted] in an ascending order.

Starting with Amendment 4 each patient will be identified in the study by a Patient Number (Patient No.) which 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 study. The Patient No. consists of the Site Number (Center No.) (as assigned by Novartis to the investigative site) and 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. Patients that previously completed Part I and reenter the study for Part II (core PoC follow-up cohort) are to be assigned a new patient number. A record of the old screening number and the new patient number is to be kept. If a patient is rescreened after being screen failed, then a new patient number is to be used. With Amendment 4, the patient number will also be captured on the eCRF.

Treatment number

If the patient is deemed eligible for enrollment into the study and will commence dosing, a treatment number will be assigned. Treatment numbers will be assigned in ascending, sequential order to eligible patients in accordance with entry into the study. The treatment number becomes the definitive subject number as soon as a patient receives the first dose of

[redacted]

the respective study treatment. Patients that previously completed the study and reenter the study after Amendment 4 (core PoC follow-up cohort) are to be assigned a new patient number. A record of the old treatment number and the new patient number is to be kept.

Once assigned to a patient, a treatment number will not be reused.

There should be a source document maintained at the site which links the screening number to the treatment assignment number (once assigned).

Patients will be assigned treatment numbers; each site will have a list of unique treatment numbers.

5.5.2 Dispensing the study treatment

Appropriate documentation of the patient specific dispensing process must be maintained.

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

5.5.3 Supply, storage and tracking of study treatment

Study drugs must be received at the study site by a designated person, handled and stored safely and properly, and kept in a secured location to which only the Investigator and designated staff have access. Upon receipt, the study drugs should be stored according to the instructions specified on the drug labels.

Storage conditions must be adequately monitored and appropriate temperature/humidity logs maintained as Source data.

The Investigator must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability ledger. Drug accountability will be noted by the Monitor during site visits and/or at the completion of the trial.

Patients will be asked to return all unused study drug and packaging at the end of the study or at the time of study drug discontinuation.

All drug supplies are to be used only for this protocol and not for any other purpose. Unless specifically instructed by Novartis, the Investigator must not destroy any drug labels, or any partly used or unused drug supply.

At the conclusion of the study, and, if allowed during the course of the study (e.g. an open label study or an un-blinded monitor), the Investigator will provide a copy of the drug accountability ledger to the Monitor.

Only after receiving a written authorization by Novartis, the Investigator will send all the unused and partly used drug supplies as well as the empty containers to the address provided at the time of authorization for destruction **or** have the unused and partly used drug supplies as well as the empty containers destroyed by the site's pharmacist, providing a drug destruction certificate.

[redacted]

5.5.3.1 Instructions for prescribing and taking study treatment

Patients will self-administer LCI699 p.o. b.i.d. in the morning and evening regardless of when they have eaten.

The investigator should promote compliance by instructing the patient to take the study drug exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the investigator if he/she is unable for any reason to take the study drug as prescribed.

The patients will also be instructed to bring back used and unused medication at selected time-points for drug accountability checking.

Patients must be instructed not to chew the medication, but to swallow it whole. All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

5.5.4 Permitted dose adjustments and interruptions of study treatment

LCI699 dose will be titrated as outlined in Section 3.1 or until normalization of UFC (below upper limit of normal, as per local lab levels). For patients who are unable to tolerate the protocol-specified dose scheme, dose adjustments are permitted. The following guidelines should be followed:

- If the patient has not reached normalization of UFC, but does not tolerate the current dose, administration of an intermediate dose between the current (untolerated) and preceding (tolerated) dose or repeated administration of the preceding, tolerated dose should be considered.
- If the patient has reached normalization of their UFC, but the current dose is no longer tolerated, an intermediate dose between the current dose and previous dose should be considered.
- If the patient had reached normalization of their UFC, but the current dose is no longer efficacious based on on-going UFC measurements, dose escalation should resume.
- If the patient has low serum cortisol or UFC < LLN, and the patient has signs/symptoms of adrenal insufficiency, a dose reduction of LCI699 should be considered.

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

5.5.5 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. Instructions for monitoring liver function, and the criteria for withholding, re-initiating, reducing dose, or discontinuing study treatment are provided in Table 5-1 below.

[redacted]

Table 5-1 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	Interrupt study drug dose. Monitor liver function tests (LFTs)[a], or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN: If resolved in ≤ 14 days, restart study drug and maintain dose level If resolved in > 14 days, then restart study drug and decrease by one dose level
> 3.0 - 10.0 x ULN*	Interrupt 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 restart study drug and 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 resolved 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 resolved 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	Interrupt 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 drug.
>10.0 – 20.0 x ULN	Interrupt 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 restart study drug and decrease by one dose level.
> 20.0 x ULN	Discontinue patient from study drug treatment 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 returned to baseline or stabilized over 4 weeks.

[redacted]

Combined [b, d] 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 x ULN] OR [AST or ALT > 8.0 x ULN], **combined with** [total bilirubin > 2 x baseline AND > 2.0 x ULN	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 resolved to baseline or stabilization over 4 weeks. Refer to Section 5.5.6 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 (ALP) (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 study drug in the situation when interrupt study drug is required for one parameter and discontinue study drug 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 (>2 x ULN and R value (ALT/ALP in x ULN) < 2) in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis 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. See Section 5.5.6 * 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.	

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

Patients with transaminase increase combined with 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.

[redacted]

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 ($R \leq 2$), hepatocellular ($R \geq 5$), 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 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.
- 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 7.2) and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

5.5.7 Rescue medication

As this is the first study to evaluate LCI699 for Cushing's disease there are no established rescue medications. If patients are not responding to, or not tolerating LCI699, they should be withdrawn from the study and other accepted therapies (surgical resection or other medications) should be initiated.

5.5.8 Concomitant treatment

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 (e)CRF.

Should a patient have an incidental and limited need for a medication to be taken within the restricted pre-dose timeframe (e.g. ibuprofen for a headache, antibiotic prophylaxis prior to dental surgery etc.), the sponsor should be advised, as administration of any concomitant medication may require the patient to be replaced. Decisions regarding replacements will be

[redacted]

discussed with the sponsor on a case-by-case basis. Administration of paracetamol, (acetaminophen) is acceptable, but must be documented.

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 e(CRF). Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

5.5.9 Prohibited treatment

Use of other drug treatments for Cushing's disease is prohibited during this study. Patients on drugs for ailments other than Cushing's disease will be checked by the Investigator against the list of known substrates of CYP1A2, CYP2D6 and CYP2E1 (see detailed list in Appendix 3). For any concomitant medications on this list, an alternate drug may be prescribed, dose adjusted of the concomitant medication as per the product label or dose limitation of LCI699 should be considered by the Investigator.

Preclinical data and preliminary clinical data indicate that there is a potential risk of QTc prolongation in humans (see Amendment 5 Rationale). Therefore, the use of medications with a "Known risk to cause TdP" and drugs 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 adequate alternative medication available, then 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 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. 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.

Investigators are advised to refer to Appendix 6 and utilize the www.crediblemeds.org website when considering the addition of a new concomitant medication, with risks of TdP, 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".

In addition, the following drugs are prohibited: spironolactone, eplerenone, and glucocorticoids (e.g., prednisone, dexamethasone). Please note the following exceptions to these prohibitions: 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 adrenal insufficiency.

[redacted]

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.

5.5.10 Concomitant medication to be use with caution

Emerging preclinical data suggest that CYP3A4/5 and CYP2D6 may be involved in LCI699 metabolism; while relative contribution of these enzymes to LCI699 metabolism *in vivo* is not yet elucidated, risk exists for drug-drug interaction with medications that are strong CYP3A4/5 and CYP2D6 inhibitors and inducers (Appendix 7). Therefore concomitant medications that are known strong inhibitors or inducers of CYP3A4/5 and CYP2D6 are to be used with caution with LCI699.

5.5.11 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 should make a reasonable effort (e.g. telephone, email, 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 he/she believes that continuation would be detrimental to the patient's well-being.

Study treatment must be discontinued under the following circumstances and according to Investigator discretion:

- Withdrawal of informed consent.
- Emergence of the following adverse events (compound specific):
  - 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:
  - hyperkalemia (serum potassium > 5.5 mmol/L; confirmed and persistent*).
  - hypokalemia (serum potassium < 3.5 mmol/L; confirmed and persistent*).
  - hyponatremia (serum sodium < 130 mmol/L; confirmed and persistent*).
- QTcF > 500 msec, if confirmed by a cardiologist (see Section 6.6.5).
- 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 6.6.5).
- Pregnancy.
- Use of any other therapy for Cushing's disease.
- Any other protocol deviation that results in a significant risk to the patient's safety.

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

[redacted]

Patients who discontinue study treatment should NOT be considered withdrawn from the study. They should return for the assessments indicated in Section 6. If they fail to return to return for these assessments for unknown reasons, reasonable effort (e.g. telephone, email, letter) should be made to contact them as specified in Section 5.5.13.

5.5.12 Withdrawal of Consent

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

- 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 subject'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 subject 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 subject'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 subject's samples until their time of withdrawal) according to applicable law.

For US 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 EU and RoW: 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.

5.5.13 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 Disposition CRF.

5.5.14 Emergency unblinding of treatment assignment

Not applicable as study is open-label.

[redacted]

5.5.15 Study completion and post-study treatment

Patient treatment in Long Term Extension-2 will end at each site within 4 months after a separate roll-over study is opened at their site, or by 31 December 2019 (whichever occurs earlier). The roll-over study will provide an opportunity of continued treatment for patients who are still ongoing at that time and who are clinically benefitting from LCI699.

Sites with the separate roll-over study option available, should arrange an End of Trial (EOT) visit within 4 months of the roll-over study opening at their site (i.e. earlier than the 6 month interval visits in Long Term Extension-2), to allow their patients to continue their LCI699 dose on this new study.

For sites where a separate roll-over study is not option, the patient may be offered a local alternative treatment option and must complete their Long-Term Extension-2 EOS visit by 31 December 2019.

The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

5.5.16 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated as described in Section 6 for a discontinued 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.

The study will be stopped if any of the following criteria are met: and no further patients enrolled pending a full safety review:

- At least 3 patients manifest a similar unexpected/off-target AE which is > CTCAE (v4) grade 2 (Appendix 5), suspected to be related to study drug and that does not resolve with drug reduction
- At least 3 patients are withdrawn from the study for adverse events as described under the individual withdrawal rules below

6 Visit schedule and assessments

The full Assessment schedules is presented before Section 1.

Patients should be seen for all visits on the designated day with a visit window of ± 2 days. Due to the circadian rhythm nature of steroid levels (including cortisol), patients are advised to come to the site on a fixed time window (e.g. ± 2 hours) for each of the visits and best efforts should be made to keep consistent throughout the study.

Patients who discontinue study treatment before completing the study, and those who discontinue from the study for any reason, should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the End of Treatment visit. In addition, an End of Study visit will be performed 28 days after the last dose administration. Every effort will be made to take the pharmacokinetic sample at the protocol specified time.

[redacted]

Patients entering the roll-over protocol will complete an EOT visit. Their EOT visit should be arranged within 4 months of the roll-over study opening at their site. For these patients the EOS visit is not applicable, as treatment on LCI699 will not be interrupted.

Patients not continuing into the roll-over protocol will complete an EOT visit upon stopping treatment, and an EOS visit 28 days after the last dose administration, must be completed by 31 December 2019. Any repeat assessments associated with this visit should be documented and followed-up appropriately by the Investigator.

6.1 Screening

Screening examinations (Visit 1) are to include the procedures found in the Assessment schedules and should occur within 74-15 days prior to Day 1. The informed consent must be signed prior to ANY screening procedure being performed. Patients that do not meet eligibility criteria are allowed to be rescreened and should be given a new patient ID number. The rescreening should be documented in the source files.

6.2 Dietary, fluid and other restrictions

During recruitment, screening/informed consent review, and baseline visit, the patients will be informed and reminded of the following restrictions:

- Patient should maintain their normal exercise regime (i.e. no new strenuous physical exercise (e.g., weight training, aerobics, football) for 7 days before dosing until after Study Completion evaluation.
- Patients should report to the site at each visit in an 8 hour fasted state. During a PK profile, patients will be provided lunch 4 hours post-dose.

6.3 Patient demographics/other baseline characteristics

Demographics

Patient demographic and baseline characteristic data to be collected on all patients include: date of birth, sex, race, predominant ethnicity.

Relevant medical history / current medical conditions

Relevant medical history and current medical conditions will be recorded on the in the CRF until the start of the study drug.

Where possible, diagnoses and not symptoms will be recorded. Cushing's disease history together with the medication/treatment used will be collected.

Any event or change in the patient's condition or health status occurring **prior to** the initial study drug administration will be reported in the Relevant medical history/Current medical conditions section of the CRF.

6.4 Treatment exposure and compliance

Treatment compliance will be determined by collecting a trough plasma PK sample at the end of the last dose (C12hr) of each b.i.d. regimen, as detailed in Section 6.7.

[redacted]

6.5 Efficacy / pharmacodynamic assessments

The following efficacy/pharmacodynamic assessments will be done using a central laboratory: UFC, plasma cortisol, plasma ACTH, salivary cortisol and aldosterone, 11-deoxycortisol, plasma and urine 11-deoxycorticosterone, plasma and urine aldosterone, plasma renin, PK, testosterone and estradiol, LH, FSH, IGF-1, urinary creatinine, urine sodium and potassium, insulin, HbA1c, TSH, free T4. Local labs can be used throughout the study for dose titrations and/or if a faster turnaround time is needed for safety reasons. Local values for UFC, plasma ACTH, plasma and urine deoxycorticosterone, testosterone and estradiol will be captured in the eCRF as applicable.

6.5.1 Mean urinary free cortisol and creatinine

The primary efficacy parameter will be urinary free cortisol. UFC will be measured in three 24-hour urine specimens collected within 7 days of day -7. The three samples will be averaged to obtain the baseline UFC level. Throughout the study, patients will collect three 24-hour urine specimens within 4 days prior to the next visit according to the Assessment schedules. If at any time, the Patient's UFC is < ULN on 2 consecutive measurements dose escalation will be halted and the patient will remain on the current efficacious dose through week 10. During the two long term extension phases, (extension-1 and extension-2) patients will collect two 24-hour urine specimens within 7 days prior to the next visit. Urine creatinine levels will also be measured to ensure validity of the 24-hour collection.

6.5.1.1 Pharmacodynamic collection and processing

Procedures for sample handling and storage will be supplied by the local and central laboratories. All sampling should have application of unique sample numbering within the sample log table contained within Appendix 1.

6.5.1.2 Pharmacodynamic analytical method(s)

Procedures for sample analysis will be supplied by the local and central laboratories and checked by Novartis personnel.

6.5.2 Plasma ACTH, plasma cortisol, 11-deoxycortisol and renin

Plasma ACTH, cortisol, 11-deoxycortisol and renin will be measured via blood samples taken at visits according to the Assessment schedules.

6.5.2.1 Pharmacodynamic collection and processing

Procedures for sample handling and storage will be supplied by the central laboratory. All sampling should have application of unique sample numbering within the sample log table contained within the Appendix 1.

6.5.2.2 Pharmacodynamic analytical method(s)

Procedures for sample analysis will be supplied by the central laboratory and checked by Novartis personnel.

[redacted]

6.5.3 Plasma and urine aldosterone and 11-deoxycorticosterone

Aldosterone and 11-deoxycorticosterone will be measured via blood and urine samples taken at visits according to the Assessment schedules.

6.5.3.1 Pharmacodynamic collection and processing

Procedures for sample handling and storage will be supplied by the central laboratory. All sampling should have application of unique sample numbering within the sample log table contained within Appendix 1.

6.5.3.2 Pharmacodynamic analytical method(s)

Procedures for sample analysis will be supplied by the central laboratory and checked by Novartis personnel.

6.5.4 Serum and urine sodium and potassium

Sodium and potassium will be measured via blood and urine samples taken at visits according to the Assessment schedules.

6.5.4.1 Pharmacodynamic collection and processing

Serum sodium and potassium will be assessed as part of the clinical chemistry panel (see Section 6.6.4.2 below) and will therefore be performed by the local lab. Procedures for sample handling and storage for urine will be supplied by the central laboratory. All sampling should have application of unique sample numbering within the sample log table contained within Appendix 1.

6.5.4.2 Pharmacodynamic analytical method(s)

Procedures for urine sample analysis will be supplied by the central laboratory and checked by Novartis personnel.

6.5.5 Salivary cortisol and aldosterone

Cortisol and aldosterone will be measured via saliva samples taken at baseline and weekly thereafter until Day 154. From Day 154 through Day 322 it will be collected every 28 days (Day 182, D210, D238, D266, D294 and D322) and from Day 322 through 490 it will be collected every 3 months (D406 and D490). During long term extension-2 samples will be collected every 3 months during the first 18 months, and every 6 months thereafter. Patients will collect a morning and evening saliva sample (upon waking and just prior to bedtime e.g., 6-8:00 and 23-24:00 respectively)

6.5.5.1 Pharmacodynamic collection and processing

Procedures for sample handling and storage will be supplied by the central laboratory. All sampling should have application of unique sample numbering within the sample log table contained within Appendix 1.

[redacted]

6.5.5.2 Pharmacodynamic analytical method(s)

Procedures for sample analysis will be supplied by the central laboratory and checked by Novartis personnel.

6.5.6 Other pharmacodynamic laboratory evaluations

Insulin will be measured via blood samples taken at visits according to the Assessment schedules. $HbA1_c$, IGF-1, TSH, free T4, LH, FSH will be collected at visits according to the Assessment schedules. Testosterone and estradiol will be collected at visits according to the Assessment schedules.

6.5.6.1 Pharmacodynamic collection and processing

Procedures for sample handling and storage will be supplied by the central laboratory. All sampling should have application of unique sample numbering within the sample log table contained within Appendix 1.

6.5.6.2 Pharmacodynamic analytical method(s)

Procedures for sample analysis will be supplied by the central laboratory and checked by Novartis personnel.

6.6 Safety

6.6.1 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 the Assessment schedules.

Information for all physical examinations must be included in the source documentation at the study site and will not be recorded the (e)CRF. Significant findings that are present prior to the start of study drug must be included in the Relevant Medical History/Current Medical Conditions screen on the patient's (e)CRF. Significant findings made after the start of study drug which meet the definition of an Adverse Event must be recorded on the Adverse Event screen of the patient's (e)CRF.

6.6.2 Vital signs

Vital signs include body temperature, BP and pulse measurements. After the patient has been sitting for 3 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. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

Body temperature will be measured at visits according to the Assessment schedules. Blood pressure and pulse rate will be measured at visits according to the Assessment schedules. If

[redacted]

vital signs are out-of-range at screening or baseline, the Investigator should obtain two additional readings, so that a total of five (5) consecutive assessments are made, with the patient seated quietly for approximately five (5) minutes preceding each repeat assessment. **At least the last reading must be within the ranges provided above in order for the patient to qualify.**

6.6.3 Height and weight

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 will be measured at visits according to the Assessment schedules.

6.6.4 Laboratory evaluations

In the case where a laboratory assessment that is listed in the inclusion/exclusion criteria is outside of a **protocol-specified range** at screening and/or at the initial baseline, the assessment may be repeated once (for the purpose of inclusion), and in any case, prior to enrollment, to rule out laboratory error. If the repeat value remains outside of protocol-specified ranges, the patient should be excluded from the study.

The following laboratory evaluations for safety will be performed locally: hematology, clinical chemistry, urinalysis (Section 6.6.4.1 to Section 6.6.4.3).

In the case where a laboratory range is **not specified by the protocol**, but is outside the reference range for the center at screening and/or initial baseline, a decision regarding whether the result is of clinical significance or not shall be made by the Investigator and shall be based, in part, upon the nature and degree of the observed abnormality. The assessment may be repeated once (for the purpose of inclusion) and in any case, prior to enrollment/randomization, to rule out laboratory error.

In all cases, the Investigator must document in the source documents, the clinical considerations (i.e., result was/was not clinically significant and/or medically relevant) in allowing or disallowing the patient to continue in the study.

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Novartis personnel. The results should be evaluated for criteria defining an adverse event and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Novartis personnel should again be contacted.

6.6.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, (monocytes, eosinophils, basophils, neutrophils, lymphocytes), and platelet count will be measured.

6.6.4.2 Clinical chemistry

Albumin, alkaline phosphatase, total bilirubin, bicarbonate/CO_2, calcium, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, chloride, creatinine, CK, γ-GT, fasting

[redacted]

plasma glucose, LDH, inorganic phosphorus, lipase, amylase, magnesium, potassium, total protein, AST, ALT, sodium,, urea/BUN and uric acid.

If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

6.6.4.3 Urinalysis

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 and blood.

6.6.5 Electrocardiogram (ECG)

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.

Twenty-four hour continuous 12-lead Holter recording with central reading of data are done on each patient according to the Assessment schedules.

Twelve-lead safety ECGs are collected at the study sites according to the Assessment schedules. 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 long term extension-1 and long term extension-2 studies, 12-lead safety ECGs will also be done according to the Assessment schedules, 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 local ECG equipment. 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 section of the CRF / eCRF.

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 eCRF will contain:

- date and time of ECG
- heart rate
- PR interval
- QT and QTc interval

[redacted]

- QRS duration

The Fridericia QT formula (QTcF) to correct for variations in heart rate should be used for clinical decisions (Fridericia 1920).

The purpose of the safety ECG is to identify patients with clinically significant ("notable" ECG abnormalities. On the day of the first study drug administration (day 1), the pre-dose ECG must be done in triplicate. The mean of the QTcF from these 3 tracings is used as the baseline QTcF to be compared with the 1.5 hour post-dose ECG on Day 1 only.

Only ECGs with clinically significant ("notable") abnormalities should be reported on the ECG tracing. A "notable abnormality" is defined as:

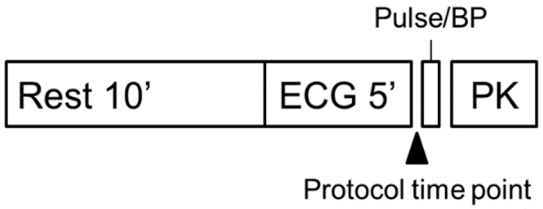
- Day 1 only: an increase in QTcF > 30msec at 1.5 hours post-dose, compared to the mean pre-dose baseline QTcF from the same day
- QTcF > 480msec with acute cardiovascular risk, as assessed by a consulting cardiologist
- Any QTcF > 500msec, confirmed by a consulting cardiologist

Notable ECG abnormalities should be recorded on the Adverse Events e(CRF) page. 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.

For any ECGs with patient safety concerns, two additional 12-lead ECGs should be performed to confirm the safety finding. 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.

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 6-1).

Figure 6-1 Sequence of cardiovascular data collection



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

QT prolongation monitoring

On the day of the first administration of LCI699 (day 1), the pre-dose baseline ECG must be done in triplicate. The mean of the QTcF values from these three ECG tracings is used to determine the mean baseline QTcF for that day only. If the safety ECG (1.5 hours post-first dose of LCI) shows an increase in QTcF > 30ms from the mean baseline value, or the QTcF is > 480ms, then the patient should be discontinued from study drug. Any ECG in doubt

[redacted]

should be reviewed promptly by a consulting cardiologist before discontinuing the patient from LCI699 therapy.

If at any follow up visit, a QTcF > 500msec is observed on the 1.5 hour post-dose safety ECG, then triplicate 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 > 500msec, 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.

If the cardiologist confirms a mean QTcF > 500msec, the patient has to discontinue according to the discontinuation procedure described in Section 5.5.9. The patient must remain under observation until the QTcF is < 480msec 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.

Otherwise, and if the cardiologist confirms, that at least one ECG shows a QTcF > 480msec, the cardiac assessments described for a confirmed QTcF > 480msec need to be followed.

If at any follow up visit a 480msec < QTcF ≤ 500msec is observed on the 1.5 hour post-dose safety ECG, the following steps need to be taken (described in Figure 6-2):

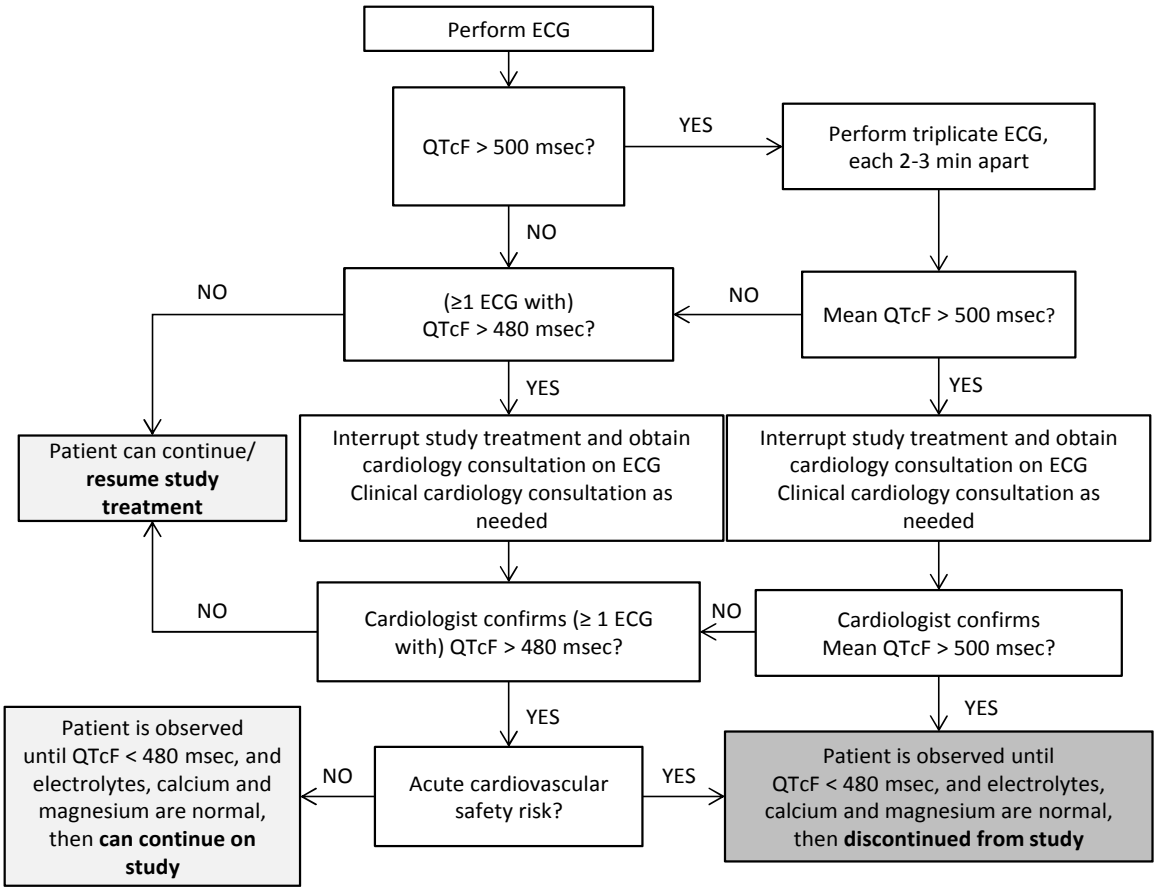
The patient has to interrupt study treatment while an urgent cardiology consultation is obtained to re-evaluate the ECG. If immediate treatment is required for patient safety this should be initiated at the study site without delay and without waiting for confirmation by a cardiologist.

- If a QTcF > 480msec is NOT confirmed, no further action needs to be taken;
- If a QTcF > 480msec is confirmed, a cardiologist must perform a thorough clinical evaluation to assess the patient for acute cardiovascular risk, and for possible underlying heart disease that needs additional evaluation and management.
    a. If based upon the assessment by the cardiologist, the investigator considers that there is an acute cardiovascular safety risk and that the subject should not continue with study medication, the subject needs to be discontinued immediately (discontinuation criteria described in Section 5.5.9).
    b. If based upon the assessment by the cardiologist, the investigator considers that there is not an acute cardiovascular safety risk, the subject can continue to receive study medication.

The patient must remain under observation until the QTcF is < 480msec and serum electrolytes, calcium, and magnesium are measured and the results are normal. This observation may be done at the site, in an Emergency Room, or a cardiology clinic, as appropriate and depending upon local resources. The results of the ECGs, cardiac examination and the recommendation by the cardiologist must be evaluated by the investigator to determine whether the subject should continue in the trial or not.

[redacted]

Figure 6-2 QT Prolongation Monitoring Flow Chart



6.6.6 Pituitary MRI

Pituitary MRI scanning with gadolinium enhancement will be performed at visits according to the Assessment schedules. These will be assessed locally to determine tumor volume and longest diameter and recorded in the eCRF. If MRI intravenous contrast is contraindicated for a patient, a non-contrast MRI scan should be performed. If MRI cannot be performed at all then a CT (with i.v. contrast if not contraindicated) may be performed. Digital copies of all imaging should be kept on site in the event Novartis requests their transfer for review/adjudication. Please see the study imaging manual for further information.

6.6.7 Pregnancy

Pregnancy tests are required of all female patients regardless of reported reproductive/menopausal status.

Serum pregnancy tests will be performed at screening, baseline and End of Study visit. Urine or serum pregnancy testing will be performed as indicated in the Assessment schedule.

[redacted]

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 and baseline, the result of this test must be received before the patient may be dosed.

6.6.8 Meal record

Not applicable.

6.7 Pharmacokinetics

6.7.1 Pharmacokinetics

The PK parameters of LCI699 to be assessed are listed in Table 6-1. Visit schedules for LCI699 PK blood collection are shown in Table 6-2.

If data allows, Ctrough,ss will be utilized as concentration at 12 h post-dose for the calculation of AUC0-12,ss and T1/2,ss. This is based on the PK principle that at steady state, Ctrough is assumed to be the same at the beginning and end of the dose interval, in this case 12 h.

Table 6-1 Non-compartmental pharmacokinetic parameters for LCI699

Cmax,ss	The maximum plasma concentration at steady state. The unit is ng/mL.
Tmax,ss	The time to reach the maximum plasma concentration at steady state. The unit is hr.
AUC0-6hr,ss	The AUC from time zero to 6 hours post dose at steady state. The unit is hr*ng/mL.
AUC0-12hr,ss	The AUC from time zero to 12 hours post dose at steady state, calculated by using the pre-dose concentration (Ctrough,ss) as the 12 hr concentration, assuming steady-state has been reached. The unit is hr*ng/mL
T1/2,ss	The elimination terminal half-life at steady-state. The unit is hr.
Ctrough,ss	The pre-dose concentration at steady-state. The unit is ng/mL.

6.7.1.1 LCI699 PK blood collection and processing

For new patients enrolled after Amendment 4 (expansion cohort), pharmacokinetic (PK) blood samples will be collected during visits on Study Day 14 (Visit 5), 28 (Visit 6), 42 (Visit 7), 56 (Visit 8) and70 (Visit 9) in the dose escalation period. Briefly, PK samples will be collected at pre-dose (0 hour), and 1, 1.5, 2, 4, 6 hour post AM dose during Visit 5 on Day 14 for the first dose level. If a patient is required to escalate to the next dose level (UFC>ULN) during the dose escalation phase of the study, then the above PK sample collection will be required again at the next visit (2 weeks after starting the next dose level). For patients who have normalized UFC, only pre-dose (trough) PK samples will be collected during the visits in the dose escalation phase of the study. (Table 6-2, PK collection No. of 2, 3, 4 or 5).

For patients re-entering the study (core PoC follow-up cohort), the 6-hr PK profile blood samples (pre-dose, 1, 1.5, 2, 4, and 6 hr post-dose) will only be collected from these patients at day 14 (Visit 5), and only pre-dose PK blood samples will be collected in the following visits 6, 7, 8 and 9.

[redacted]

From Day 70 through Day 154, only pre-dose (trough) PK samples will be collected from all patients during visits on Study Day 98 (Visit 10), 126 (Visit 11), and 154 (Visit 777).

PK parameters of LCI699 will be determined (if feasible) by Phoenix WinNonlin using noncompartmental analysis (Table 6-1).

Table 6-2 PK blood sampling for LCI699

PK Sample No	PK Collection No	Treatment Period	Visit No	Study Day	Time (hrs post dose)[b]	Volume (mL)
7	1	1	5	14	0(pre-dose)[a]	2
8	1	1	5	14	1	2
9	1	1	5	14	1.5	2
10	1	1	5	14	2	2
11	1	1	5	14	4	2
12	1	1	5	14	6	2
13	2	1	6	28	0(pre-dose)[a]	2
14	2	1	6	28	1	2
15	2	1	6	28	1.5	2
16	2	1	6	28	2	2
17	2	1	6	28	4	2
18	2	1	6	28	6	2
19	3	1	7	42	0(pre-dose)[a]	2
20	3	1	7	42	1	2
21	3	1	7	42	1.5	2
22	3	1	7	42	2	2
23	3	1	7	42	4	2
24	3	1	7	42	6	2
25	4	1	8	56	0(pre-dose)[a]	2
26	4	1	8	56	1	2
27	4	1	8	56	1.5	2
28	4	1	8	56	2	2
29	4	1	8	56	4	2
30	4	1	8	56	6	2
31	5	1	9	70	0(pre-dose)[a]	2
32	5	1	9	70	1	2
33	5	1	9	70	1.5	2
34	5	1	9	70	2	2
35	5	1	9	70	4	2
36	5	1	9	70	6	2
37	6	2	10	98	0(pre-dose)[a]	2
38	7	2	11	126	0(pre-dose)[a]	2
39	8	2	777	154	0(pre-dose)[a]	2

[a] Samples will be collected prior to the AM dose of LCI699
[b] Deviations for the following PK assessment times are acceptable based on logistical and operational considerations: ± 5 min for time-points up to and including 2 hours; ± 10 min for time-points up to and including 6 hours.

[redacted]

All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. A total of 2 mL of venous blood will be collected at each time point into K2-EDTA-containing polyethylene tubes.

Immediately after blood is drawn, the tube should be inverted gently several times to ensure the mixing of contents (e.g., anticoagulant). Avoid prolonged sample contact with the rubber stopper. Tubes should be stored on wet ice until centrifuged. Within 60 minutes, centrifuge the sample between 3 and 5°C for 10 minutes at approximately 1500 g. Immediately after centrifugation, transfer a minimum of 0.7 ml plasma into 2 ml conical polypropylene screw-cap tubes (Sarstedt, part# 72.693) followed by proper mixing and put on dry ice. The labels will be provided by the site. The tubes will be kept frozen at approximately -60°C pending on shipment on dry ice for analysis. Note: the specified tubes are required for automation compatibility. No substitutions are permissible. The samples should be shipped to the central laboratory of the study as indicated in the laboratory manual.

The exact clock time of dosing, as well as actual sample collection date and time will be entered on the PK blood collection summary page of the CRF. Sampling problems will be noted in the relevant field of the CRF.

The plasma samples for the pharmacokinetic profile must be labeled according to the central laboratory requirements:

Labels will be provided by the central laboratory. The exact clock time of dosing will be entered on the dose administration page of the CRF, and the actual sample collection date and time will be entered on the PK blood collection summary page of the CRFs. Sampling problems will be noted in the relevant field of the CRF.

6.7.2 Urine collection and processing

Not applicable.

6.7.3 Pharmacokinetic analytical method(s)

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 limit of quantitation will be 0.05 ng/mL for plasma. Copies of the first 5% of the standard curves and sample chromatograms or instrument printouts will be included along with a summary of the analytical method. Data will be provided to demonstrate that the assay method has the required specificity, accuracy, precision, limits of quantification, linearity, recovery, and stability for LCI699 in plasma.

[redacted]

[redacted]

7 Safety monitoring

7.1 Adverse events

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after obtaining informed consent even if the event is not considered to be related to study drug. Study drug includes the investigational drug under evaluation and the comparator drug or placebo that is given during any phase of the study. Medical conditions/diseases present before obtaining informed consent are only considered adverse events if they worsen. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, or are considered clinically significant, or require therapy.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered

by the patient during or between visits or through physical examination, laboratory test, or other assessments. All adverse events must be recorded on the Adverse Events e(CRF) with the following information:

1. the severity grade CTC grade 1 – 4.
2. its relationship to the study drug(s) (suspected/not suspected).
3. its duration (start and end dates or if continuing at final exam).
4. whether it constitutes a serious adverse event (SAE).

An SAE is defined as an event which:

- is fatal or life-threatening.
- results in persistent or significant disability/incapacity.
- constitutes a congenital anomaly/birth defect.
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - 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 the start of study drug.
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission.
  - social reasons and respite care in the absence of any deterioration in the patient's general condition.
- 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.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 7.2.

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication given; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged. The action taken to treat the adverse event should be recorded on the Adverse Event e(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 drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or will be communicated between IB updates 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.

[redacted]

7.2 Serious adverse event reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until 28 days after the patient has stopped study participation (defined as time of last dose of study drug taken or last visit whichever is later) must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 28 day period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is 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. The investigator must assess the relationship of any SAE to study drug, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the local Novartis Drug Safety and Epidemiology Department. The telephone and telecopy number of the contact persons in the local department of Clinical Safety and Epidemiology, 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 person 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. 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 or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, a Drug Safety and Epidemiology 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.

7.3 Pregnancies

To ensure patient safety, each pregnancy in a patient on study drug 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 local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study drug of 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 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and (e)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 (e)CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study drug 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 on (e)CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (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 (e)CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the (e)CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

[redacted]

8.3 Database management and quality control

Novartis staff or CRO working on behalf of Novartis review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data.

Concomitant 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 will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

The occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be made available for data analysis.

9 Data analysis

9.1 Analysis sets

The 12 Cushing's disease patients who were enrolled in the study prior to Amendment 4 are considered as core PoC cohort. Patients who re-enter the study after Amendment 4 are considered as core PoC follow-up cohort. The 15 new patients enrolled after Amendment 4 are considered as expansion cohort.

Core PoC cohort:

Safety analysis set (SAS): all patients that received at least one dose of study drug prior to Amendment 4.

The SAS will be applied for both efficacy and safety analyses for Core PoC.

PK analysis set: all patients with at least one dose of study drug and at least one post-dose PK assessment prior to Amendment 4.

Core PoC follow-up cohort:

Full analysis set (FAS): all patients who are re-entering the study after Amendment 4.

Safety analysis set (SAS): all patients that received at least one dose of study drug after re-entering the study.

PK analysis set: all patients with at least one dose of study drug and at least one post-dose PK assessment after re-entering the study.

Expansion cohort:

Full analysis set (FAS): all patients who were enrolled in the study after Amendment 4. Safety analysis set (SAS): all patients who received at least one dose of study drug.

The SAS will be applied for both efficacy and safety analyses for the expansion cohort. The FAS will be applied for the listing purpose.

PK analysis set: all enrolled patients with at least one dose of study drug and at least one post-dose PK assessment.

9.2 Demographics and other baseline characteristics

Summary statistics will be provided for demographics and baseline characteristics. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum and maximum will be provided. All data for background and demographic variables will be listed.

Relevant medical history, current medical conditions, results of laboratory screens and any other relevant information will be listed.

9.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

Descriptive statistics will be used to summarize the total dose of study medication. Concomitant medications will be summarized by ATC class, preferred term by both primary and secondary safety analysis sets, by means of frequency and percentages. Study drug administration, concomitant medication will also be listed.

9.4 Analysis of the primary variable(s)

The primary objective of the study is to assess the effects of 10 weeks treatment of LCI699 on UFC in patients with Cushing's disease for the core PoC cohort. The primary analysis will be based on the Week 10 mean UFC level treating response as a binary outcome for the patients included in the core PoC cohort.

9.4.1 Variable

The primary variable is defined as the proportion of responders to LCI699 at week 10. A patient is considered to be a responder if the mean UFC level (at least two 24 hour measurements) from the Week 10 is ≤ ULN or represents a ≥50% decrease from baseline. Patients who discontinue for a disease or treatment related reason (e.g. death, adverse event, clinical disease progression etc.), or whose mean Week 10 24-hour UFC levels are higher than the normal limit and experience <50% decrease in UFC are classified as non-responders. Patients who have <2 baseline or post-baseline 24-hour UFC measurement will not be included in the primary analyses.

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

9.4.2 Statistical model, hypothesis, and method of analysis

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

9.4.3 Handling of missing values/censoring/discontinuations

Missing values will not be imputed.

9.4.4 Supportive analyses

The urine creatinine will be checked to ensure that the 24 hour urine collection is complete.

The proportion of responders among patients with one or more 24 hour measurements for both baseline and Week 10 will be estimated and the 95% confidence interval will be provided. If a patient has no UFC collections at the Week 10 visit, the UFC evaluation for that patient at the preceding visit will be used.

Summary statistics of UFC levels at each visit will be presented. A paired t-test will be performed to compare Week 10 and baseline mean 24 hour UFC. Mean 24 hour UFC will be log-transformed prior to the analysis. Point estimate and the associated 95% confidence interval for the ratio of geometric means (Week 10/baseline) will be obtained from the paired t-test. Salivary cortisol at midnight and other times of the day will be analyzed similarly.A second responders analysis will be performed to determine the proportion of patients who normalize their UFC in response to LCI699 (achieve a mean week 10 UFC ≤ ULN).

Additionally, the proportion of patients with at-least one (Week 2 to Week 8) or mean (Week 10) UFC measurement that is ≤ULN or represents a greater than 50% reduction from baseline will be determined.

[redacted]

9.5 Analysis of secondary variables

9.5.1 Pharmacodynamics

Core PoC cohort

Plasma ACTH, aldosterone, renin, glucose, insulin, HOMA, and serum cortisol, sodium and potassium measurements will be summarized by visit. A paired t-test will be performed to compare Week 10 and baseline for each endpoint. Measurements will be log-transformed prior to the analysis. Point estimate and the associated 95% confidence interval for the ratio of geometric means (Week 10/baseline) will be obtained from the paired t-test.

Core PoC follow-up cohort & Expansion cohort

The following analyses will be conducted separately for each of the two cohorts (Core PoC follow-up and Expansion).

The proportion of responders at Weeks 10 and 22 will be summarized using point estimates and 95% CIs (Exact Method). Analyses will be based on the SAS. If mUFC is missing a particular time point, then the value will not be imputed but the patient will be considered a non-responder at that time point.

In addition, responders will be further classified as controlled and partially controlled.

Descriptive summaries will be generated for the change from the respective baselines to different time points in mUFC, plasma ACTH, serum cortisol, steroid hormones, tumor volume, SBP, DBP, weight, BMI, lipids, HbA1c and FPG. 95% CIs will also be provided for the changes from baseline.

9.5.2 Escape analysis

Only patients who attained UFC normalization during the study will be included in the escape analysis, where escape is defined as the loss of UFC control (i.e. UFC > ULN) on at least 2 consecutive visits at the highest tolerated dose after previously attaining UFC normalization. “First-time escape” is used to describe the first occurrence of 2 consecutive visits with uncontrolled UFC at the patient’s highest tolerated dose after attaining UFC normalization. Time to escape is defined as the number of weeks from the visit of first UFC normalization (mUFC <= 1x ULN) to the first visit of first-time escape. For patients who have no safety issue, 30 mg bid is the highest tolerated dose. For patients who have dose reduction due to safety reasons, the resulting reduced dose will be the highest tolerated dose. For patients who discontinue the study due to AEs, the dosage at discontinuation will be considered the highest tolerated dose. For all other situations, patients will be considered as not reaching their highest tolerated dose.

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

[redacted]

In addition, time to escape will be summarized using descriptive statistics by cohort for patients who meet escape criteria.

9.5.3 Safety

Safety analyses will be done separately for core PoC cohort, expansion cohort and core PoC follow-up cohort.

Vital signs

All vital signs data will be listed by patient and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by visit/time.

ECG evaluations

All ECG data will be listed by patient and visit/time, abnormalities will be flagged. Summary statistics will be provided by visit/time.

Standard clinical laboratory evaluations

All laboratory data will be listed by patient and visit/time. Abnormalities will be flagged. Summary statistics will be provided by visit/time.

Special clinical laboratory evaluations

All laboratory data will be listed by patient and visit/time and if ranges are available abnormalities will be flagged. Summary statistics will be provided by visit/time.

Adverse events

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

The number and percentage of patients with adverse events will be tabulated by body system and preferred term. A patient with multiple adverse events within a body system is only counted once towards the total of this body system.

Concomitant medications / significant non-drug therapies

All concomitant therapies will be listed by patient.

9.5.4 Health-related quality of life

Not applicable.

9.5.5 Pharmacokinetics

All completed patients with plasma concentration will be included in the pharmacokinetic data analysis. Pharmacokinetic analysis of this unblinded study may be performed at any time during the study, including prior to database lock. The steady-state PK parameters including

[redacted]

Cmax, Tmax, AUC0-6hr, AUC0-12hr, T1/2 and Ctrough levels will be summarized using descriptive statistics.

Plasma concentrations will be expressed in ng/mL. All concentrations below the limit of quantification or missing data will be labeled as such in the concentration data listings. Concentrations below the limit of quantification will be treated as zero in summary statistics.

[redacted]

9.5.7 Other biomarkers

Not applicable.

9.5.8 PK/PD

Relationship between LCI699 exposure and PD variables (including QTcF) will be explored by graphical approach and descriptive statistics will be provided. Additional statistical analysis such as ANOVA or linear or nonlinear regression analysis will be performed, if necessary. PK/PD analyses may be reported separately, if appropriate.

9.6 Sample size calculation

Assuming that response rates of less than or equal to 15% are not acceptable, and that response rates greater than or equal to 50% are good indication of a beneficial effect, data from 12 to 15 patients will provide 70% to 84% power to reject the null hypothesis of 15% response rate when the alternative hypothesis of a 50% response rate is true based on an exact (binomial) test for single proportion at a significance level of 0.05. The expected drop out rate is <20% and drop outs may be replaced to ensure a minimum of 12 completers. The estimated response rate (%) along with the 95% confidence interval based on the Exact Bionmial Test for each possible outcome in the study are provided in the table below.

[redacted]

Table 9-1 Precision level (95% confidence interval for each response rate) in the study

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

The 15 patients in the expansion cohort will also afford the same level of precision around the estimate of the responder rate at Month 6, as shown in Table 9-1.

9.7 Power for analysis of key secondary variables

Not applicable.

9.8 Interim analyses

Because this is an open label study, response to the therapy will be monitored as the study proceeds. In addition, an interim analysis will be performed after the first12 patients complete 10 weeks of treatment (core PoC cohort) and a CSR will be generated from this data. Additional interim analyses may be conducted for the expansion cohort and the core-PoC follow-up cohort. Additional database locks may be conducted to provide data to support the market authorization applications for LCI699.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and 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, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

[redacted]

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. 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.

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

Women of child bearing potential should be informed that taking the study drug 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.

[redacted]

In the event that Novartis wants to perform testing on the samples that are not described in this protocol, additional Institutional Review Board and/or ethics committee approval will be obtained.

10.3 Responsibilities of the investigator and IRB/IEC

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) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to Novartis before study initiation. 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

[redacted]

required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 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 trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

11 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 trial 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 it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

11.1 Protocol Amendments

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. Only amendments that are required for patient safety may be implemented prior to IRB/IEC 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 within 10 working days.

12 References (available upon request)

Bochicchio D, Losa M, Buchfelder M, et al (1995); Factors influencing the immediate and late outcome of Cushing's disease treated by transsphenoidal surgery: a retrospective study by the European Cushing's Disease Survey Group. Journal of Clinical Endocrinology and Metabolism; 80, 3114-3120.

Estrada J, Boronat M, Mielgo M, et al. (1997). The Long-Term Outcome Of Pituitary Irradiation After Unsuccessful Transsphenoidal Surgery In Cushing's Disease. N Engl J Med 1997; 336:172-7.

Fridericia L (1920). The duration of systole in the electrocardiogram of normal subjects and of patients with heart disease. Acta Medica Scandinavica (53): 469–486.

Losa M, Picozzi P, Redaelli G, et al. Pituitary Radiotherapy for Cushing's Disease. Neuroendocrinology 2010;92 v(suppl 1):107–110.

Masri-Iraqui H, Robenshtok E, et al (2014). Elevated white blood cell counts in Cushing's disease: association with hypercortisolim. Pituitary 2014 Oct; 17(5):436-40.

Minniti G, Osti M, Jaffrain-Rea M, et al. Long-term follow-up results of postoperative radiation therapy for Cushing's disease.ffJ Neurooncol (2007) 84:79–84.

Sonino N, Zielezny M, Fava G, et al (1996); Risk factors and long-term outcome in pituitary-dependent Cushing's disease. Journal of Clinical Endocrinology and Metabolism; 81, 2647-2652.

[redacted]

13 Appendices

13.1 Appendix 1: Sample Log table - all matrices

Sample Log: Time schedule for sampling for safety bloods, pharmacokinetic (PK), pharmacodynamic (PD), [redacted]

[redacted]

Visit no.	Time	Safety 10mL	Plasma LCI699 PK 2mL	LCI699 PK Collection No	Sample No	Plasma ACTH 4mL	Sample No	Plasma cortisol 3mL	Sample No	Plasma renin 3mL	Sample No	Plasma Aldosterone 3mL	Sample No	Plasma Deoxycorticosterone, 11-deoxycortisol 7ml	Sample No
1	Screening	x													
2	Baseline	x				x[1]	301	x	308	x	315	x	401	x	408
3	Day 1	x													
5	Day 14	x	x 6	1	7 to 12	x	302	x	309	x	316	x	402	x	409
6	Day 28	x	x 6*	2	13 to 18	x	303	x	310	x	317	x	403	x	410
7	Day 42	x	x 6*	3	14 to 24	x	304	x	311	x	318	x	404	x	411
8	Day 56	x	x 6*	4	25 to 30	x	305	x	312	x	319	x	405	x	412

[redacted]

Visit no.	Time	Safety 10mL	Plasma LCI699 PK 2mL	LCI699 PK Collection No	Sample No	Plasma ACTH 4mL	Sample No	Plasma cortisol 3mL	Sample No	Plasma renin 3mL	Sample No	Plasma Aldosterone 3mL	Sample No	Plasma Deoxycorticosterone, 11-deoxycortisol, 7ml	Sample No
9	Day 70	x	x 6*	5	31 to 36	x	306	x	313	x	320	x	406	x	413
10	Day 98	x	x	6	37	x	350	x	361	x	372	x	450	x	461
11	Day 126	x	x	6	38	x	351	x	362	x	373	x	451	x	462
V777	Day 154	x	x	6	39	x	352	x	363	x	374	x	452	x	463
13	Day 182	x				x	353	x	364	x	375	x	453	x	464
14	Day 210	x				x	354	x	365	x	376	x	454	x	465
15	Day 238	x				x	355	x	366	x	377	x	455	x	466
16	Day 266	x				x	356	x	367	x	378	x	456	x	467
17	Day 294	x				x	357	x	368	x	379	x	457	x	468
18	Day 322	x				x	358	x	369	x	380	x	458	x	469
19	Day 406	x				x	359	x	370	x	381	x	459	x	470
V777	Day 490	x				x	360	x	371	x	382	x	460	x	471
21-26	Every 3 months[X]	x				x	2383-2388,	x	2389-2394	x	2395-2400	x	2472,-2477	x	2478-2483
27,28,29,..	Every 6 months	x				x	2501, 2502,2503,...	x	2601,2602,2603,...	x	2701,2702,2703,...	x	2801,2802,2803, ...	x	2901, 2902,2903,...
V777	(EOT-2)	x				x	1100	x	1102	x	1103	x	1104	x	1105
V778	EOS	x				x	307	x	314	x	321	x	407	x	414

[redacted]

Visit no.	Time	Safety 10mL	Plasma LCI699 PK 2mL	LCI699 PK Collection No	Sample No	Plasma ACTH 4mL	Sample No	Plasma cortisol 3mL	Sample No	Plasma renin 3mL	Sample No	Plasma Aldosterone 3mL	Sample No	Plasma Deoxycorticosterone, 11-deoxycortisol, 7ml	Sample No
999	Unscheduled				2001		3001		4001		5001		6001		7001

* PK samples to be collected at (1) pre-dose (0 hour), 1, 1.5, 2, 4 and 6 hours post AM dose for escalation dose or (2) pre-dose (trough) for maintained dose
[1] to be collected between day-14 and day-7
[X] to be collected every 3 months for the first 18 months and then every 6 months until EOT extension-2

Visit no.	Time	free T4, TSH, LH, FSH, 7.5mL	Sample No	HbA1C, 2mL	Sample No	Insulin, 3.5mL	Sample No	Testosterone 2mL	Sample No	Estradiol 2mL	Sample No	IGF-1 6mL	Sample No
1	Screening							x	426	x	433		
2	Baseline	x[1]	415	x[1]	417	x	419	x	427	x	434	x	440
3	Day 1												
5	Day 14					x	420	x	428	x	435		
6	Day 28					x	421	x	429	x	436		
7	Day 42					x	422	x	430	x	437		
8	Day 56					x	423	x	431	x	438		
9	Day 70	x	416	x	418	x	424	x	502	x	514	x	441
10	Day 98	x	472			x	491	x	503	x	515	x	526

[redacted]

Visit no.	Time	free T4, TSH, LH, FSH, 7.5mL	Sample No	HbA1C, 2mL	Sample No	Insulin, 3.5mL	Sample No	Testosterone 2mL	Sample No	Estradiol 2mL	Sample No	IGF-1 6mL	Sample No
11	Day 126	x	473			x	492	x	504	x	516	x	527
V777	Day 154	x	474	x	484	x	493	x	505	x	517	x	528
13	Day 182	x	475			x	494	x	506	x	518	x	529
14	Day 210	x	476			x	495	x	507	x	519	x	530
15	Day 238	x	477	x	485	x	496	x	508	x	520	x	531
16	Day 266	x	478			x	497	x	509	x	521	x	532
17	Day 294	x	479	x	486	x	498	x	510	x	522	x	533
18	Day 322	x	480	x	487	x	499	x	511	x	523	x	534
19	Day 406	x	481	x	488	x	500	x	512	x	524	x	535
V777	Day 490	x	482	x	489	x	501	x	513	x	525	x	536
21-26	Every 3 months	x	2538-2543	x	2544-2549	x	2550-2555	x	2556-2561	x	2562-2567	x	2568-2573
27,28,29 …	Every 6 months	x	2574,2575,2576…	x	2577,2578,2579…	x	2580,2581,2582…	x	2583,2584,2585…	x	2586,2587,2588…	x	2589,2590,2591…
EOT-EXT-2	EOT	x	1110	x			1111		1114		1115		1116
V778	EOS	x	483			x	425	x	432	x	439	x	537

[1] to be collected between day-14 and day-7

[X] to be collected every 3 months for the first 18 months and every 6 months until EOT for extension-2

[redacted]

Urine Log: Time schedule for urine sampling pharmacodynamic (PD)

Study Phase			Urine Aldosterone (5ml)	Sample Number	Urine Sodium/ Potassium (20ml)	Sample Number	Urine deoxycorticosterone (5ml)	Sample Number
Treatment	Day	Time						
Baseline	Day -14 to 0	n/a	x	101	x	108	x	116
Treatment	Day 1	0-24 hr pre am dose D1			x	109		
Treatment	Day 14	Pre-dose[1]	x	102	x	110	x	117
Treatment	Day 28	Pre-dose[1]	x	103	x	111	x	118
Treatment	Day 42	Pre-dose[1]	x	104	x	112	x	119
Treatment	Day 56	Pre-dose[1]	x	105	x	113	x	120
Treatment	Day 70	Pre-dose[1]	x	106	x	114	x	121
Treatment	Day 98	Pre-dose[1]	x	150	x	161	x	172
Treatment	Day 126	Pre-dose[1]	x	151	x	162	x	173
Treatment	Day 154	Pre-dose[1]	x	152	x	163	x	174
Extension-	Day 182	Pre-dose[1]	x	153	x	164	x	175
Extension-1	Day 210	Pre-dose[1]	x	154	x	165	x	176
Extension-1	Day 238	Pre-dose[1]	x	155	x	166	x	177
Extension-1	Day 266	Pre-dose[1]	x	156	x	167	x	178
Extension-1	Day 294	Pre-dose[1]	x	157	x	168	x	179
Extension-1	Day 322	Pre-dose[1]	x	158	x	169	x	180
Extension-1	Day 406	Pre-dose[1]	x	159	x	170	x	181

[redacted]

Study Phase			Urine Aldosterone (5ml)	Sample Number	Urine Sodium/ Potassium (20ml)	Sample Number	Urine deoxycorticosterone (5ml)	Sample Number
Treatment	**Day**	**Time**						
Baseline	Day -14 to 0	n/a	x	101	x	108	x	116
Extension-1	Day 490	n/a	x	160	x	171	x	182
Extension-2[x]	Every 3 months	Pre-dose[1]		2186-2191	x	2192-2197	x	2198-2203
Extension-2[x]	Every 6 months	Pre-dose[1]		2204,2205,2206…	x	2207,2208,2209…	x	2210,2211,2212…
Ext-2 EoT	EOT	Pre-dose[1]		1201	x	1202	x	1203
EOS	EOS	n/a		107	x	115	x	122
1= urine sample collected for the 24 hours prior to am dose of clinic visit X= to be collected every 3 months for the first 18 months and every 6 months until EOT for extension-2								

[redacted]

Saliva Log: Time schedule for saliva sampling pharmacodynamic (PD)

Study Phase		Saliva Sample			
Treatment	**Day**	**Time**	**Sample No**	**Time**	**Sample No**
Baseline	-14	06-08:00	601	23-24:00	602
Baseline	-7	06-08:00	615	23-24:00	616
Baseline	-1	06-08:00	627	23-24:00	628
Treatment	6	06-08:00	639	23-24:00	640
Treatment	13	06-08:00	653	23-24:00	654
Treatment	20	06-08:00	667	23-24:00	668
Treatment	27	06-08:00	681	23-24:00	682
Treatment	34	06-08:00	695	23-24:00	696
Treatment	41	06-08:00	709	23-24:00	710
Treatment	48	06-08:00	723	23-24:00	724
Treatment	55	06-08:00	737	23-24:00	738
Treatment	62	06-08:00	751	23-24:00	752
Treatment	69	06-08:00	765	23-24:00	766
Treatment	76	06-08:00	779	23-24:00	780
Treatment	83	06-08:00	793	23-24:00	794
Treatment	90	06-08:00	797	23-24:00	798
Treatment	97	06-08:00	799	23-24:00	800
Treatment	104	06-08:00	801	23-24:00	802
Treatment	111	06-08:00	803	23-24:00	804
Treatment	118	06-08:00	805	23-24:00	806
Treatment	125	06-08:00	807	23-24:00	808
Treatment	132	06-08:00	809	23-24:00	810
Treatment	139	06-08:00	811	23-24:00	812
Treatment	146	06-08:00	813	23-24:00	814
Treatment	153	06-08:00	815	23-24:00	816
Ext-1	181	06-08:00	817	23-24:00	818
Ext-1	209	06-08:00	819	23-24:00	820
Ext-1	237	06-08:00	821	23-24:00	822
Ext-1	265	06-08:00	823	23-24:00	824
Ext-1	293	06-08:00	825	23-24:00	826
Ext-1	321	06-08:00	827	23-24:00	828
Ext-1	405	06-08:00	829	23-24:00	830
Ext-1	489	06-08:00	831	23-24:00	832
Ext-2	Every 3 months	06-08:00	2835-2840	23-24:00	2841-2846
Ext-2	Every 6 months	06-08:00	2847,2848,2849…	23-24:00	2850,2851,2852…
EOT- Ext-2	n/a	06-08:00	1301	23-24:00	1302
EOS	n/a	06-08:00	833	23-24:00	834

[redacted]

13.2 Appendix 2: Sample labeling and shipping information

Labels will need to be provided by the central laboratory. No added label should cover the original label.

The Sample Numbers are reported in the Blood / Urine Log table in Appendix 1.

Detailed instructions for collection, handling, storage and shipment of samples are outlined in the [CLCI699C2201 Central Laboratory Manual].

PK blood samples will be shipped to the central laboratory where they will be stored and finally forwarded to the following address for bioanalysis:

[redacted],
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936, USA

[redacted]

13.3 Appendix 3: Possible drug-drug interactions with LCI699

CYP2E1	CYP1A2	CYP2D6
enflurane	amitriptyline	tamoxifen
halothane	caffeine	carvedilol
isoflurane	clomipramine	S-metoprolol
methoxyflurane	clozapine	propafenone
sevoflurane	cyclobenzaprine	timolol
acetaminophen	estradiol	amitriptyline
chlorzoxazone	fluvoxamine	clomipramine
ethanol	haloperidol	desipramine
N,N-dimethylformamide	imipramine	fluoxetine
theophylline	mexiletine	imipramine
	naproxen	paroxetine
	olanzapine	haloperidol
	ondansetron	perphenazine
	phenacetin	risperidone
	acetaminophen	thioridazine
	propranolol	zuclopenthixol
	riluzole	alprenolol
	ropivacaine	amphetamine
	tacrine	aripiprazole
	theophylline	atomoxetine
	tizanidine	bufuralol
	verapamil	chlorpheniramine
	(R)warfarin	chlorpromazine
	zileuton	codeine
	zolmitriptan	debrisoquine
		dexfenfluramine
		dextromethorphan
		donepezil
		duloxetine
		encainide
		flecainide
		fluvoxamine
		lidocaine
		metoclopramide
		methoxyamphetamine
		mexiletine
		minaprine
		nebivolol
		nortriptyline
		ondansetron
		oxycodone
		perhexiline
		phenacetin
		phenformin

[redacted]

CYP2E1	CYP1A2	CYP2D6
		promethazine
		propranolol
		sparteine
		tramadol
		venlafaxine

[redacted]

13.4 Appendix 4: Determination of body mass index (weight[kg] / height[m]^2)

Height (m)	Weight (kg)																							
	46	**48**	**50**	**52**	**54**	**56**	**58**	**60**	**62**	**64**	**66**	**68**	**70**	**72**	**74**	**76**	**78**	**80**	**82**	**84**	**86**	**88**	**90**	**92**
1.44	22.2	23.1	24.1	25.1	26.0	27.0	28.0	28.9	29.9	30.9	31.8	32.8	33.8	34.7	35.7	36.7	37.6	38.6	39.5					
1.46	21.6	22.5	23.5	24.4	25.3	26.3	27.2	28.1	29.1	30.0	31.0	31.9	32.8	33.8	34.7	35.7	36.6	37.5	38.5	39.4				
1.48	21.0	21.9	22.8	23.7	24.7	25.6	26.5	27.4	28.3	29.2	30.1	31.0	32.0	32.9	33.8	34.7	35.6	36.5	37.4	38.3	39.3			
1.50	20.4	21.3	22.2	23.1	24.0	24.9	25.8	26.7	27.6	28.4	29.3	30.2	31.1	32.0	32.9	33.8	34.7	35.6	36.4	37.3	38.2	39.1		
1.52	19.9	20.8	21.6	22.5	23.4	24.2	25.1	26.0	26.8	27.7	28.6	29.4	30.3	31.2	32.0	32.9	33.8	34.6	35.5	36.4	37.2	38.1	39.0	
1.54	19.4	20.2	21.1	21.9	22.8	23.6	24.5	25.3	26.1	27.0	27.8	28.7	29.5	30.4	31.2	32.0	32.9	33.7	34.6	35.4	36.3	37.1	37.9	38.8
1.56	18.9	19.7	20.5	21.4	22.2	23.0	23.8	24.7	25.5	26.3	27.1	27.9	28.8	29.6	30.4	31.2	32.1	32.9	33.7	34.5	35.3	36.2	37.0	37.8
1.58	18.4	19.2	20.0	20.8	21.6	22.4	23.2	24.0	24.8	25.6	26.4	27.2	28.0	28.8	29.6	30.4	31.2	32.0	32.8	33.6	34.4	35.3	36.1	36.9
1.60	18.0	18.8	19.5	20.3	21.1	21.9	22.7	23.4	24.2	25.0	25.8	26.6	27.3	28.1	28.9	29.7	30.5	31.3	32.0	32.8	33.6	34.4	35.2	35.9
1.62		18.3	19.1	19.8	20.6	21.3	22.1	22.9	23.6	24.4	25.1	25.9	26.7	27.4	28.2	29.0	29.7	30.5	31.2	32.0	32.8	33.5	34.3	35.1
1.64		17.8	18.6	19.3	20.1	20.8	21.6	22.3	23.1	23.8	24.5	25.3	26.0	26.8	27.5	28.3	29.0	29.7	30.5	31.2	32.0	32.7	33.5	34.2
1.66			18.1	18.9	19.6	20.3	21.0	21.8	22.5	23.2	24.0	24.7	25.4	26.1	26.9	27.6	28.3	29.0	29.8	30.5	31.2	31.9	32.7	33.4
1.68			17.7	18.4	19.1	19.8	20.5	21.3	22.0	22.7	23.4	24.1	24.8	25.5	26.2	26.9	27.6	28.3	29.1	29.8	30.5	31.2	31.9	32.6
1.70				18.0	18.7	19.4	20.1	20.8	21.5	22.1	22.8	23.5	24.2	24.9	25.6	26.3	27.0	27.7	28.4	29.1	29.8	30.4	31.1	31.8

[redacted]

Height (m)	Weight (kg)																						
	46	**48**	**50**	**52**	**54**	**56**	**58**	**60**	**62**	**64**	**66**	**68**	**70**	**72**	**74**	**76**	**78**	**80**	**82**	**84**	**86**	**88**	**90**	**92**
1.72				17.6	18.3	18.9	19.6	20.3	21.0	21.6	22.3	23.0	23.7	24.3	25.0	25.7	26.4	27.0	27.7	28.4	29.1	29.7	30.4	31.1
1.74					17.8	18.5	19.2	19.8	20.5	21.1	21.8	22.5	23.1	23.8	24.4	25.1	25.8	26.4	27.1	27.7	28.4	29.1	29.7	30.4
1.76						18.1	18.7	19.4	20.0	20.7	21.3	22.0	22.6	23.2	23.9	24.5	25.2	25.8	26.5	27.1	27.8	28.4	29.1	29.7
1.78						17.7	18.3	18.9	19.6	20.2	20.8	21.5	22.1	22.7	23.4	24.0	24.6	25.2	25.9	26.5	27.1	27.8	28.4	29.0
1.80							17.9	18.5	19.1	19.8	20.4	21.0	21.6	22.2	22.8	23.5	24.1	24.7	25.3	25.9	26.5	27.2	27.8	28.4

Appendix 4: Determination of body mass index (cont. from previous page)

1.82							17.5	18.1	18.7	19.3	19.9	20.5	21.1	21.7	22.3	22.9	23.5	24.2	24.8	25.4	26.0	26.6	27.2	27.8
1.84								17.7	18.3	18.9	19.5	20.1	20.7	21.3	21.9	22.4	23.0	23.6	24.2	24.8	25.4	26.0	26.6	27.2
1.86									17.9	18.5	19.1	19.7	20.2	20.8	21.4	22.0	22.5	23.1	23.7	24.3	24.9	25.4	26.0	26.6
1.88										18.1	18.7	19.2	19.8	20.4	20.9	21.5	22.1	22.6	23.2	23.8	24.3	24.9	25.5	26.0
1.9											18.3	18.8	19.4	19.9	20.5	21.1	21.6	22.2	22.7	23.3	23.8	24.4	24.9	25.5
1.92												18.4	19.0	19.5	20.1	20.6	21.2	21.7	22.2	22.8	23.3	23.9	24.4	25.0
1.94													18.6	19.1	19.7	20.2	20.7	21.3	21.8	22.3	22.9	23.4	23.9	24.4

[redacted]

Appendix 4: Determination of body mass index (cont. from previous page)

Height (m)	Weight (kg)																				
	92	94	96	98	100	102	104	106	108	110	112	114	116	118	120	122	124	126	128	130	132
1.44																					
1.46																					
1.48																					
1.50																					
1.52																					
1.54	38.8	39.6																			
1.56	37.8	38.6	39.4																		
1.58	36.9	37.7	38.5	39.3																	
1.60	35.9	36.7	37.5	38.3	39.1																
1.62	35.1	35.8	36.6	37.3	38.1	38.9															
1.64	34.2	34.9	35.7	36.4	37.2	37.9	38.7	39.4													
1.66	33.4	34.1	34.8	35.6	36.3	37.0	37.7	38.5	39.2												
1.68	32.6	33.3	34.0	34.7	35.4	36.1	36.8	37.6	38.3	39.0	39.7										
1.70	31.8	32.5	33.2	33.9	34.6	35.3	36.0	36.7	37.4	38.1	38.8										
1.72	31.1	31.8	32.4	33.1	33.8	34.5	35.2	35.8	36.5	37.2	37.9	38.5	39.2								
1.74	30.4	31.0	31.7	32.4	33.0	33.7	34.4	35.0	35.7	36.3	37.0	37.7	38.3								
1.76	29.7	30.3	31.0	31.6	32.3	32.9	33.6	34.2	34.9	35.5	36.2	36.8	37.4	38.1							
1.78	29.0	29.7	30.3	30.9	31.6	32.2	32.8	33.5	34.1	34.7	35.3	36.0	36.6	37.2	37.9						
1.80	28.4	29.0	29.6	30.2	30.9	31.5	32.1	32.7	33.3	34.0	34.6	35.2	35.8	36.4	37.0	37.7					

[redacted]

Appendix 4: Determination of body mass index (cont. from previous page)

1.82	27.8	28.4	29.0	29.6	30.2	30.8	31.4	32.0	32.6	33.2	33.8	34.4	35.0	35.6	36.2	36.8	37.4				
1.84	27.2	27.8	28.4	28.9	29.5	30.1	30.7	31.3	31.9	32.5	33.1	33.7	34.3	34.9	35.4	36.0	36.6	37.2			
1.86	26.6	27.2	27.7	28.3	28.9	29.5	30.1	30.6	31.2	31.8	32.4	33.0	33.5	34.1	34.7	35.3	35.8	36.4	37.0	37.6	
1.88	26.0	26.6	27.2	27.7	28.3	28.9	29.4	30.0	30.6	31.1	31.7	32.3	32.8	33.4	34.0	34.5	35.1	35.6	36.2	36.8	37.3
1.90	25.5	26.0	26.6	27.1	27.7	28.3	28.8	29.4	29.9	30.5	31.0	31.6	32.1	32.7	33.2	33.8	34.3	34.9	35.5	36.0	36.6
1.92	25.0	25.5	26.0	26.6	27.1	27.7	28.2	28.8	29.3	29.8	30.4	30.9	31.5	32.0	32.6	33.1	33.6	34.2	34.7	35.3	35.8
1.94	24.4	25.0	25.5	26.0	26.6	27.1	27.6	28.2	28.7	29.2	29.8	30.3	30.8	31.4	31.9	32.4	32.9	33.5	34.0	34.5	35.1
1.96	23.9	24.5	25.0	25.5	26.0	26.6	27.1	27.6	28.1	28.6	29.2	29.7	30.2	30.7	31.2	31.8	32.3	32.8	33.3	33.8	34.4

13.5 Appendix 5: Summary of Common Toxicity Criteria for Adverse Events v4.0 (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.

[redacted]

13.6 Appendix 6: 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.

[redacted]

13.7 Appendix 7: List of drugs to be used with caution with LCI699

Drugs in the following list have the potential to alter LCI699 drug exposure, and should be used with caution when co-administered with LCI699.

Table 13-1 List of strong CYP3A4/5 and CYP2D6 inhibitors and inducers

Strong inhibitors of CYP3A4/5		
Generic Name	**Brand Name**	**Class**
clarithromycin	Biaxin®	Antibiotic
telithromycin	Ketek®	Antibiotic
troleandomycin	Tao®	Antibiotic
indinavir	Crixivan®	Protease inhibitor
lopinavir	Kaletra®	Protease inhibitor
nelfinavir	Viracept®	Protease inhibitor
ritonavir	Norvir®	Protease inhibitor
saquinavir	Fortovase®; Invirase®	Protease inhibitor
tipranavir	Aptivus®	Protease inhibitor
itraconazole	Onmel®; Sporanox®	Anti-fungal
ketoconazole	Nizoral®	Anti-fungal
posaconazole	Noxafil®	Anti-fungal
voriconazole	Vfend®	Anti-fungal
boceprevir	Victrelis®	Anti-viral
telaprevir	Incivek®	Anti-viral
cobicistat	Stribild®	Enzyme inhibitor
conivaptan	Vaprisol®	Diuretic
elvitegravir	Stribild®	Integrase inhibitor
nefazodone	Serzone®	Antidepressant
Strong inducers of CYP3A4/5		
Generic Name	**Brand Name**	**Class**
carbamazepine	Carbatrol®; Epitol®; Equetro®; Tegretol®; Teril®	Antiepileptic
mitotane	Lysodren®	Anti-neoplastic
phenobarbital	Luminal®; Solfoton®	Anticonvulsant
phenytoin	Dilantin®	Antiepileptic
rifabutin	Mycobutin®	Antibiotic
rifampin (rifampicin)	Rifadin®; Rifamate®; Rifater®; Rimactane®	Antibiotic
St. John's wort (hypericum perforatum)	N/A	Herbal supplement

Strong inhibitors of CYP2D6		
Generic Name	**Brand Name**	**Class**
bupropion	Aplenzin®; Forfivo XL®; Wellbutrin®; Zyban®	Antidepressant; smoking cessation
fluoxetine	Prozac®; Sarafem®; Symbyax®	Antidepressant
paroxetine	Paxil®; Pexeva®	Antidepressant
quinidine	Nuedexta®	Anti-arrhythmic

[redacted]