COR-2017-OLE Protocol Cover Page

Study Title:	An Open-Label Extension Study of Levoketoconazole (2S,4R-Ketoconazole) in the Treatment of Endogenous Cushing's Syndrome
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EudraCT No.	2017-004647-20

CORTENDO

CLINICAL STUDY PROTOCOL

An Open-Label Extension Study of Levoketoconazole (2S,4R-ketoconazole) in the Treatment of Endogenous Cushing's Syndrome

Protocol Number	COR-2017-OLE
Compound	Levoketoconazole
IND No.	115968
EudraCT No.	2017-004647-20
Phase	3
Dates:	
Amendment 2	23 September 2019
Amendment 1	19 July 2018
Original	26 March 2018
Sponsor	Cortendo AB 900 Northbrook Drive, Suite 200 Trevose, Pennsylvania, 19053 USA
	Cortendo AB c/o TMF Sweden AB Sergels Torg 12 111 57 Stockholm Sweden

Revision Chronology

26 March 2018	Original
19 July 2018	Amendment 1: • Removal of Data Monitoring Committee requirement for OPTICS Study • Clarified / corrected inconsistencies and typographical errors throughout protocol • Section 1.2, paragraph 3 added to the last sentence - at time of entry into the current study). • Clarified subjects' participation may continue for at least 3 years. • Clarified unit of measure for serum potassium is mEq/L • Simplified and condensed wording of Inclusion Criteria throughout the protocol • Addition of Inclusion Criterion for subjects who completed COR-2012-01 or COR-2017-01 but had a break in therapy and the specification of washout periods for drugs taken for Cushing's Syndrome • Clarified timing of Screening / Baseline assessments for subjects that had a break in therapy • Section 5.2 – In addition, subjects must…. – minor text modification • Table 2 Title modified to read Expected Normal 24-Hour Creatinine Excretion from Adequate Urine Collections • Modified text in Section 6.2.5.1, paragraph 6 - Due to the muscle wasting observed in CS and dependent on the length of the disease, subjects may have 24-hour urine creatinine excretion rates below the values reported in **Table 2** [Petersenn 2013]. Creatinine excretion values that are somewhat below the normative value will be considered indicative of adequate collection when urine volume is adequate. Note that the above values were derived from populations of generally healthy individuals without kidney dysfunction. • Section 7 – added bullet to read - Levoketoconazole should usually be taken at

	approximately the same times each day, and for the most consistent day-to-day absorption, should be ingested with the same types of liquids and/or foods each day (see Section 8.2). • Section 7 – 2nd bullet modified to read - Consumption of grapefruit, lime juice and Seville oranges (aka sour orange, bigarade orange, or marmalade orange) and its products should be limited to once weekly owing to potential drug interactions with levoketoconazole that may influence its bioavailability; • Section 10.1 modified Title to read Common Permitted Medications • Section 10.1, Paragraph 2 – modified text to read – For management of hypokalemia, **slow-released** potassium…. • Section 10.1, Paragraph 7 – deleted **anti-inflammatory** • Modified text in Section 12.5, paragraph 2 • Section 14.1.1 modified text to read - If the subject is receiving doses greater than 150 mg/day, persistent and presumed study medication-related QTc changes may be managed by temporarily withholding study medication if deemed necessary. Note that a prolonged QTc interval that is less than 500 msec may not always warrant temporary medication stoppage, depending on patient-specific clinical factors, e.g. if the QTc does not exceed normal reference values (ULN for men is 440 msec and for women is 460 msec). • Section 14.1.2, Paragraph 1- modified text to read - If a persistent and confirmed levoketoconazole-related QTc interval prolongation above 500 msec as defined in Section 6.2.3 is identified, the Investigator should attempt to manage such QTc prolongations by temporarily stopping study medication followed by dose reduction if doing so does not eliminate the benefits of treatment. If therapeutic benefit cannot be maintained following dose reduction for drug-induced QTc prolongation above 500 msec, study medication

	should be stopped permanently and the subject should be withdrawn. • Section 14.1.2, Paragraph 2 – modified text to read - If a persistent and confirmed levoketoconazole-related QTc interval prolongation above 500 msec is observed at the lowest levoketoconazole dose (150 mg/day), administration of levoketoconazole should stop permanently and the subject should be withdrawn. • Section 14.1.2 – Paragraph 3 added to read - Persistent, confirmed levoketoconazole-related QTc interval prolongation that represents an increase greater than 60 msec from baseline but that may not be of sufficient duration to cause concern of arrhythmias (e.g. less than 440 msec in men or less than 460 msec in women), depending on other clinical factors (e.g. recalcitrant hypokalemia) need not be managed with dosage reduction or result in withdrawal. • Addition of Subject Diary to Appendix A • Addition of LDH to Appendix A, footnote 14 • Addition of LDH to Appendix B • Modified text in Appendix I, paragraph 2 to specify where prohibited medications are categorized into more than one category, the most restrictive category should hold precedent. • Added Ammonia to Appendix N: Instructions for Liver Function Test Abnormalities Follow-up, item 10. • Removal of reference to obtaining PK sample and clarification of 'possible' study treatment interruption in Appendix N. • Addition of Administer drug and/or drug accountability at Dose Adjustment / Safety Monitoring Visit to Appendix A.

23 September 2019	Amendment 2: • Corrected typographical and formatting errors. • Updates made to ensure consistency of wording and alignment of information between the Protocol Synopsis and the Protocol, as well as alignment between sections of the protocol. • Addition of lactic acid dehydrogenase to List of Abbreviations and Definition of Terms • Section 1.2, added a sentence at the end to read: Certain subjects that were enrolled in Study COR-2017-01 when randomization was closed or subjects with a gap in treatment with levoketoconazole may require re-establishment or establishment of a Therapeutic Dose. As a result, dose titration may be required as outlined in Section 8.2. • Section 5.1, modified item 2 NOTE to read: Subjects meeting criteria 1 or 2 above who have had a break in therapy may be eligible only after discussion with the Medical Monitor. If eligible, such subjects may require re-establishment of the Therapeutic Dose via titration. All subjects who have had a break in therapy should be discussed with the Medical Monitor to determine the starting dose of levoketoconazole. • Section 5.1, added item 5 to read: Achieved a clinically meaningful partial response (with reduction in UFC) in Study COR-2017-01 at dose level 7 or at a maximally tolerated dose of levoketoconazole but did not meet the randomization criteria for Study COR-2017-01 at the end of the Dose Titration and Maintenance Phase when randomization was open. • Section 5.1, modified item 6 to read: Were levoketoconazole-naïve prior to entry and were enrolled in Study COR-2017-01 in the Dose Titration and Maintenance Phase when randomization was closed. (NOTE: Such subjects must receive at least 1 dose of levoketoconazole before transitioning to this study). • Section 6.2.5.1, modified paragraph 5 to read: Note that the above values were derived from

	populations of generally healthy individuals without kidney dysfunction. Due to the muscle wasting observed in CS and dependent on the length of the disease, subjects may have 24-hour urine creatinine excretion rates below the values reported in **Table 2** [Petersenn 2013]. Therefore, creatinine excretion values that are somewhat below the normative value will be considered indicative of adequate collection when urine volume is adequate. The Medical Monitor will provide guidance as to the adequacy of the collection. • Section 8.2, added paragraph 4 to read: For subjects that have had a gap in treatment with levoketoconazole prior to entry in COR-2017-OLE, re-establishment or establishment of a subject's Therapeutic Dose at the baseline visit may be necessary and, as a result, dose titration may be required. Subjects that were in the Dose Titration and Maintenance Phase of Study COR-2017-01 when randomization was closed may also require establishment of a Therapeutic Dose. In both of these instances, the Investigator will consult with the Medical Monitor to determine the starting dose of levoketoconazole. Subsequent dose increases to the subject's previously established Therapeutic Dose or Maximally Tolerated Dose should not exceed 150 mg/day per occasion and should occur no more frequently than once every 2 weeks unless otherwise agreed with the Medical Monitor or designee. • Section 12.5.5 Table 4, deletion of third column (Flag) • Addition of footnote 16 to Appendix A to clarify subject diary dispensing at Screening Visit. • Addition of Dispense Drug to Appendix A. • Removal of reference to INR evaluations from Section 14.2. • Removal of the word 'without' from the last text box on the top line of the Recommended LFT Management Guidance in Appendix N.

SPONSOR APPROVAL

An Open-Label Extension Study of Levoketoconazole (2S,4R-ketoconazole) in the Treatment of Endogenous Cushing's Syndrome

Fredric Cohen, MD
Chief Medical Officer

[redacted]

INVESTIGATOR AGREEMENT

I have read this protocol and agree:

- To conduct the study as outlined herein, in accordance with current International Council for Harmonization (ICH) Tripartite Guideline on Good Clinical Practice (GCP), the Declaration of Helsinki and comply with the obligations and requirements of Clinical Investigators and all other requirements listed in 21 CFR part 312 and in accordance with the study procedures provided by Cortendo and local regulations.
- Not to implement any changes to the protocol without prior agreement from the Sponsor and prior review and written approval from the Investigational Review Board (IRB) or Independent Ethics Committee (IEC), except as would be necessary to eliminate an immediate hazard to study subject(s), or for administrative aspects of the study.
- To ensure that all persons assisting me with the study are adequately informed about the investigational product(s) and of their study-related duties as described in the protocol.
- I agree to completely inform all subjects in this study concerning the pertinent details and purpose of the study prior to their agreement to participate in the study in accordance with GCP and regulatory authority requirements.
- I will be responsible for maintaining each subject's consent form in the study file and providing each subject with a signed copy of the consent form.
- That I am thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, and any additional information provided to me by, or on behalf of Cortendo.

Investigator Name and Title:

Institution/Address:

Contact Information:

Signature: _____ **Date:** _____

PROTOCOL SYNOPSIS

Name of Sponsor/Company: Cortendo AB

Name of Investigational Product: Levoketoconazole (previously COR-003)

Name of Active Ingredient: (2S,4R)-(-)-cis-Ketoconazole
{2S,4R cis-1-acetyl-4-[4-[2-(2,4-dichlorophenyl)-2-(IH-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl] methoxylphenyl] piperazine}

Title of Study: An Open-Label Extension Study of Levoketoconazole (2S,4R-ketoconazole) in the Treatment of Endogenous Cushing's Syndrome

Study center(s): This is a multicenter study at approximately 50 sites in North America, Europe and the Middle East.

Phase of development: Phase 3

Objective:

The objective of this study is to assess long-term safety and efficacy durability of levoketoconazole as chronic treatment for endogenous Cushing's Syndrome (CS).

Criteria for evaluation:

When calculating changes from Baseline for efficacy evaluations, Baseline will be either or both of:

- Open-label extension (OLE) study Baseline;
- The original parent study COR-2012-01 [SONICS] or COR-2017-01 [LOGICS]) Baseline;

With the choice of Baseline described in the Statistical Analysis Plan for each endpoint/analysis.

Exploratory efficacy endpoints:

- Proportions of subjects with mean urinary free cortisol (mUFC): 1) Less or equal to the upper limit of normal (ULN) of the reference range; 2) Above the ULN to 1.5X the ULN; and 3) Above 1.5X the ULN;
- Changes from Baseline in markers of cortisol including mUFC and late night salivary cortisol (LNSC);
- Proportion of subjects with LNSC above the ULN of the reference range;
- Changes from Baseline in Clinical Signs and Symptoms of CS, health-related quality of life (QoL), and symptoms of depression;
- Changes from Baseline in biomarkers of CS comorbidities (fasting blood glucose [FBG], fasting insulin, homeostatic model assessment-insulin resistance [HOMA-IR], hemoglobin A1c [HbA1c], blood pressure, total cholesterol, high-density lipoprotein-cholesterol [HDL-C], low-density lipoprotein-cholesterol [LDL-C], high-sensitivity C-reactive protein [hsCRP]);
- Frequency of usage and changes from Baseline in frequency of usage of anti-diabetic, anti-cholesterol and anti-hypertensive therapies;
- Compliance (adherence) and persistence with therapy per tablet counts.

Safety endpoints:

Safety will be assessed by incidence and severity of Adverse Events (AEs), Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESIs) as well as by physical examinations, safety laboratory panels (including adrenocorticotrophic hormone [ACTH], liver function tests [LFTs], blood chemistry, hematology), electrocardiograms (ECGs) (to include assessment of the QTc interval), vital signs and pituitary Magnetic Resonance Imaging (MRI) for subjects with a history of a pituitary tumor.

Overall Design and Plan: This is a long-term, OLE study of levoketoconazole in subjects with endogenous CS who have completed one or both parent studies or otherwise potentially qualify for this study, as defined in the entry criteria.

Long-term safety, tolerability, and efficacy data will be collected at intervals consistent with recognized standards of care.

Subjects will remain on the previously established Therapeutic Dose of levoketoconazole that they were last receiving prior to entry into this OLE study unless a change in dose is medically indicated. Certain subjects that were enrolled in Study COR-2017-01 when randomization was closed or subjects with a gap in treatment with levoketoconazole may require re-establishment or establishment of a Therapeutic Dose. As a result, dose titration may be required, and the Investigator will consult with the Medical Monitor to determine the starting dose of levoketoconazole. Any planned dose increase of levoketoconazole above the previously established Therapeutic Dose will require the Medical Monitor's prior approval and will require unplanned visits or additional evaluations to investigate the etiology underlying the need for higher dose levels. If approved, dose increases will generally be made as 150 mg/day and no more frequently than once every 2 weeks, and will be accompanied by clinical examination and laboratory tests to assure and document safe use. Dose decreases may be made as needed for reasons of safety or tolerability and will be documented but do not require prior Medical Monitor approval.

The study comprises Screening and Baseline Visits followed by office visits every 3 months. Dose Adjustment/Safety Monitoring Visits will also be conducted in the event of a need for a dose increase of levoketoconazole during the study.

Screening and Baseline Visits

Subjects entering directly from a parent study: The visit schedule for this OLE study can overlap with those of the parent studies to ensure a smooth transition to the OLE study with no break in levoketoconazole usage.

Extension Study COR-2017-OLE Visit:	Screening	Baseline
Can overlap with	⇩	⇩
Parent Study COR-2012-01 (SONICS) visit:	Month 9 (M9)	Month 12 (M12)
Parent Study COR-2017-01 (LOGICS) visit:	Restoration Phase Visit 1 (RES1)	Restoration Phase Visit 2 (RES2)

If necessary, the OLE Screening assessments may be conducted at a separate Screening Visit that must be completed approximately 3-4 weeks prior to the final visit of the parent study whenever feasible.

If a subject is unable to have the OLE Baseline assessments performed at the final regularly scheduled visit of the parent study, the Screening and Baseline procedures may be performed at a separate Baseline Visit.

In some cases, subjects may have a gap between completing a parent study and enrolling in this study that may in some cases involve a break in treatment. For subjects who have completed a parent study within 6 months, the Screening Phase will rely primarily on data collected during the parent study and completed with data collected in OPTICS. In order for the Screening and Baseline visit to be combined, the ECG, LNSCs and LFTs must be obtained within 2 weeks of the Screening/Baseline visit and UFCs must be obtained within 6 weeks of the Screening/Baseline visit.

Subjects entering this study following a break in therapy of **greater than or equal to six months** will undergo all Screening and Baseline procedures as outlined in Appendix A.

Regular Study Visits

Regular visits should occur every 3 months (+/- 7 days) or more often as necessary for enhanced safety monitoring (e.g. if a dose increase is required). Some procedures, however, are required only every 6 months, and MRIs are required annually and only for subjects with history of a pituitary tumor. The timings of each assessment are shown in the Time and Events Table (Appendix A).

Number of subjects (planned): Up to 60 subjects are anticipated to be enrolled.

Inclusion Criteria:

To be eligible for participation in this study, subjects for whom the investigator believes long-term use of levoketoconazole may be beneficial must meet **ONE** of the following criteria:

1. Completed the Extended Evaluation Phase of Study COR-2012-01 (i.e. M12).
2. Completed the Restoration Phase of Study COR-2017-01 (i.e. RES2).

   NOTE: Subjects meeting criteria 1 or 2 above who have had a break in therapy may be eligible only after discussion with the Medical Monitor. If eligible, such subjects may require re-establishment of the Therapeutic Dose via titration. All subjects who have had a break in therapy should be discussed with the Medical Monitor to determine the starting dose of levoketoconazole. Prior to resuming treatment with levoketoconazole, other therapies for Cushing's syndrome must undergo an appropriate washout period, with minimum washout durations as follows:

   - Ketoconazole or metyrapone: 2 weeks;
   - Dopamine agonists: bromocriptine (2 weeks), cabergoline (8 weeks);
   - Octreotide acetate LAR, lanreotide Autogel®, pasireotide LAR: 12 weeks;
   - Lanreotide SR: 8 weeks;
   - Octreotide acetate (immediate release) or short-acting pasireotide: 1 week;
   - Mifepristone (RU 486, KORLYM®): 4 weeks;
   - Megestrol acetate or medroxyprogesterone acetate (and selected other synthetic progestins): 6 weeks.

3. Currently in a named patient program or other Expanded Access Program receiving levoketoconazole.
4. Were levoketoconazole-naïve prior to entry and received early rescue therapy with open-label levoketoconazole in Study COR-2017-01.
5. Achieved a clinically meaningful partial response (with reduction in UFC) in Study COR-2017-01 at dose level 7 or at a maximally tolerated dose of levoketoconazole but did not meet the randomization criteria for Study COR-2017-01 at the end of the Dose Titration and Maintenance Phase when randomization was open.
6. Were levoketoconazole-naïve prior to entry and were enrolled in Study COR-2017-01 in the Dose Titration and Maintenance Phase when randomization was closed. (**NOTE**: Such subjects must receive at least 1 dose of levoketoconazole before transitioning to this study.)

In addition, subjects must meet **ALL** the following criteria:

1. Willing to participate and able to provide written informed consent prior to any study procedures being performed; eligible subjects must be able to understand the informed consent form prior to inclusion into the study.
2. A female is eligible to enter and participate in the study if she is:
3. Postmenopausal, defined as age 50 years or older with amenorrhea for more than 1 year or any age with serum follicle stimulating hormone (FSH) at least 23 mIU/mL and estradiol no more than 40 pg/mL (140 pmol/L) (**NOTE**: laboratory values obtained during COR-2012-01 or COR-

2017-01 protocol will be utilized).
OR

4. Surgically sterile—documented hysterectomy and/or bilateral oophorectomy or tubal ligation.
OR
5. Of child-bearing potential and agrees to use a highly effective method of birth control while participating in the study and for 30 days after the last dose of levoketoconazole. Abstinence is considered acceptable birth control if routinely practiced.
Fertile men must also agree to use a highly effective method of birth control while participating in the study and for 90 days after the last dose of levoketoconazole. Abstinence is considered acceptable birth control if routinely practiced.
6. Able to comprehend and comply with procedures.

Exclusion Criteria:

Subjects will not be eligible for participation in the study if **ANY** of the following criteria are met:

1. Discontinued levoketoconazole while participating in Study COR-2012-01 or Study COR-2017-01 or a named patient program or other Expanded Access program, due to safety or tolerability concerns or lack of efficacy.
2. Pregnant, lactating or intend to conceive while receiving levoketoconazole.
3. Have a medical condition or other circumstances that, in the opinion of the Investigator, might interfere with the subject's participation or pose unacceptable risk to the subject.
4. Scheduled for surgical treatment of CS or received surgical treatment of CS within the 6 weeks prior to Screening.
5. Had non-CS major surgery within the 4 weeks prior to Screening.
6. Treated with mitotane within 6 months prior to enrollment.
7. History of malignancy, including adrenal or pituitary carcinomas (other than low-risk, well-differentiated carcinomas of thyroid, breast or prostate that are very unlikely to require further treatment in the opinion of the treating physician, or squamous cell or basal cell carcinoma of the skin).
8. QTc interval greater than 470 msec via central-reader interpretation during Screening.
9. Clinically significant abnormality in 12-lead electrocardiogram (ECG) during Screening requiring medical intervention (may be eligible once stable, to be determined case by case).
10. Clinical or radiological signs of compression of the optic chiasm newly apparent since enrolling in a parent study.
11. Liver safety tests during the Screening Phase as follows:
    - ALT and/or AST above 3X ULN (NOTE: transaminase values up to 5X ULN may be allowed on an exceptional basis for subjects who have exhibited stable values for at least 3 months)
    - AP or TBN above 2X ULN.
        - Subjects with isolated indirect TBN up to 3X ULN that are presumed to have Gilbert's syndrome may be enrolled if all other liver safety tests are within normal levels.
12. Decreased renal function as defined by eGFR below 40 mL/min/1.73 m^2, using MDRD equation for eGFR.
13. Serum potassium below 3.9 mEq/L (may be supplemented to achieve 3.9 mEq/L or above).
14. Abnormal free thyroxine (FT4), unless subsequently corrected and stable for at least 4 weeks. Subjects with thyroid stimulating hormone (TSH) less than the lower limit of normal (LLN) and normal FT4 are potentially eligible without intervention.
15. Abused alcohol or drugs since enrolling in a parent study (in the Investigator's opinion).

16. Currently participating in another study or has received any investigational treatment (drug, biological agent or device) other than levoketoconazole, within prior 30 days of the Screening visit or five half-lives of treatment, whichever is longer.
17. Current use of any H2-receptor antagonists, proton-pump inhibitors, or sucralfate (all inhibit absorption of levoketoconazole; subjects may be allowed to enroll after washout). [NOTE: A list of acceptable oral antacids will be provided; if used, antacids must be ingested at least 2 hours **after** dosing of levoketoconazole.]
18. Current use of any prohibited concomitant medication that cannot be discontinued safely and washed out completely prior to the Baseline Visit, including but not limited to the following (a more complete list is included in Appendix I):
    - Drugs used to treat Cushing's Syndrome;
    - Weight loss medications (prescription or over the counter);
    - Acetaminophen (paracetamol) above 2 g total daily dose;
    - Strong **inducers or inhibitors** of CYP3A4 enzyme system that may interfere with the metabolism of levoketoconazole and cannot be discontinued prior to first dose;
    - Herbal preparations: St John's Wort, echinacea, gingko, goldenseal, yohimbe, red yeast rice, danshen, Silybum marianum, Asian ginseng, Schissandra sphenanthera, shankhapushpi, and Asian herb mixture (Xiao chai hu tang and saiboku-to);
    - Topical or inhaled corticosteroids (other than low potency products to be discussed with Medical Monitor first);
    - Carbamazepine;
    - Drugs that pose unacceptable risk due to overlapping or exaggerated toxicities or pharmacological action due to presumed pharmacokinetics (PK) or pharmacodynamic (PD) interactions with levoketoconazole.

Investigational product, dosage and mode of administration:

Levoketoconazole (2S,4R-ketoconazole); 150-mg immediate release tablets for oral administration. Doses of levoketoconazole can range from a total daily dose of 150 mg up to 1200 mg. Levoketoconazole will be administered daily, approximately every 12 hours, per the individual Therapeutic Dose previously established for each eligible subject during the parent study or as subsequently modified. The minimum daily dose is 150 mg once a day for subjects who cannot tolerate 150 mg twice a day. Dose increases should not be more than 150 mg/day and should occur no more frequently than once every 2 weeks unless first approved by the Medical Monitor or the designee.

Duration of treatment:

There is no predefined completion timeframe for this OLE study, and interim analyses may be performed at the Sponsor's discretion. Subjects may continue receiving or discontinue levoketoconazole based on the medical judgement of the Investigator while the study remains open. It is anticipated that subjects' participation may continue for at least 3 years.

Reference therapy, dosage and mode of administration:

Not applicable.

Analysis Population:

Intent-to-Treat (ITT) Population: The ITT population will include all subjects who provide informed consent and receive at least one dose of levoketoconazole in this OLE study. This population will be used for the analyses of safety and efficacy.

Statistical methods:

The overall strategy will be to evaluate the changes or shifts in the efficacy endpoints relative to the OLE and original parent study Baselines, as applicable. All efficacy endpoints are considered exploratory. Results will also be compared between the two parent studies, as applicable. Given that this is a single-arm OLE study with exploratory efficacy endpoints only, there is no formal hypothesis to be tested, and the sample size to be enrolled is not pre-determined.

The primary analysis approach for the exploratory efficacy endpoints will be to calculate point estimates and construct two-sided 95% confidence intervals. P-values from statistical tests for significance will be calculated for descriptive purposes only. For continuous endpoints, the change from each of the two Baselines to each regular visit in the OLE study, including the final visit, will be calculated. The 95% confidence interval for the mean changes and corresponding p-values will be calculated using paired t-tests. For categorical endpoints, the shifts from each of the two Baselines to each regular visit in the OLE study, including the final visit, will be presented. The 95% confidence interval for differences in the paired proportions will be calculated using the adjusted Wald method, and the shifts will be evaluated for significance using McNemar's test or Bowker test of symmetry. The mean changes from Baseline to each regular visit will be compared between the parent studies using unpaired t-test for continuous endpoints, and the proportions at each regular visit will be compared between the parent studies using Fisher's Exact test for categorical endpoints.

Interim analyses may be performed at the Sponsor's discretion.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACTH	Adrenocorticotropic hormone
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
AP	Alkaline Phosphatase
AST	Aspartate aminotransferase
βhCG	Beta human chorionic gonadotropin
BDI-II	Beck Depression Inventory
BMI	Body mass index
CFR	Code of Federal Regulations
CD	Cushing's disease
CRF	Case Report Form
CRP	C-reactive protein
CS	Cushing´s syndrome
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DST	Dexamethasone Suppression Test
ECG	Electrocardiogram/electrocardiograph
eGFR	Estimated glomerular filtration rate
FBG	Fasting blood glucose
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
FT4	Free thyroxine
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GR	Glucocorticoid receptor
HbA1c	Hemoglobin A1C
HDL-C	High-density lipoprotein-cholesterol
HOMA-IR	Homeostatic model assessent – insulin resistance
HR	Heart rate
hsCRP	High-sensitivity C-reactive protein
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational new drug
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent-to-treat
LDH	Lactic acid dehydrogenase
LDL-C	Low-density lipoprotein-cholesterol
LFT	Liver function test
LLN	Lower limit of normal
LNSC	Late night salivary cortisol
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume

MDRD	Modified Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MR	Mineralocorticoid receptor
MRI	Magnetic Resonance Imaging
mUFC	Mean Urinary Free Cortisol
NCI CTCAE	National Cancer Institute Common Terminology for Adverse Events
OGTT	Oral glucose tolerance test
OLE	Open-label extension
PD	Pharmacodynamic
PK	Pharmacokinetics
PT	Prothrombin time
PTT	Prothromboplastin time
QoL	Quality of life
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected using Bazett's correction
QTcF	QT interval corrected using Fridericia's correction
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SPM	Study procedures manual
TBN	Total bilirubin
TEAE	Treatment-emergent adverse event
TSH	Thyroid stimulating hormone
UFC	Urinary free cortisol
ULN	Upper limit of normal
US	United States
WBC	White blood cell

1 INTRODUCTION

1.1 Background

Levoketoconazole is currently being evaluated in two Phase 3 studies. Study COR-2012-01 (also known as SONICS) is a single-arm, open-label, dose titration and maintenance study to assess efficacy, safety, tolerability, and pharmacokinetics (PK) of levoketoconazole in subjects with endogenous Cushing's Syndrome (CS). Following initial Screening and washout periods, as applicable, SONICS comprises three treatment phases: a Dose Titration Phase to achieve an effective and tolerable maximum dose (i.e., the Therapeutic Dose) lasting approximately 2 to 21 weeks; a Maintenance Phase of 6 months treatment at the Therapeutic Dose, and an Extended Evaluation Phase of 6 months of continued treatment. Levoketoconazole is administered as 150 mg immediate release tablets for oral twice daily dosing; total daily dose is titrated in 150 mg increments from a starting dose of 300 mg up to a maximal daily dose of 1200 mg. Ninety-four (94) subjects were enrolled into the Dose Titration Phase of Study COR-2012-01 with a goal of at least 70 subjects completing the 6-month Maintenance Phase.

Study COR-2017-01 (also known as LOGICS) is a double-blind, randomized, placebo-controlled withdrawal following single-arm, open-label levoketoconazole study to assess efficacy, safety, tolerability, and PK of levoketoconazole in subjects with endogenous CS. A blinded-treatment Restoration Phase is included for subjects who do not require early rescue and tolerate the 8-week blinded, randomized-withdrawal through to completion. Study methodology varies by cohort prior to randomization only. Approximately 35 subjects will be enrolled into the Randomized Withdrawal Phase of the study to provide at least 26 study completers (either completed all visits in the Randomized Withdrawal Phase or required early rescue).

Please refer to the Investigator's Brochure (IB) for a detailed description of all preclinical and clinical studies conducted with levoketoconazole.

1.2 Rationale Supporting Long-term Study of Levoketoconazole

As most medically treated CS patients receive life-long drug therapy, it is to the advantage of medical practice to obtain as much long-term data in the setting of a carefully monitored clinical trial setting as feasible. Individual study subjects benefit directly via their participation. Continued access to an investigational drug that appears to be working well is desirable, particularly when the few commercially available drugs for chronic treatment of CS have been used previously without satisfactory results, the situation of many subjects enrolled in the parent studies.

The emerging safety profile of levoketoconazole supports its use in an open-label extension (OLE) study (OPTICS). Aggregate safety data from Study COR-2012-01 has been reviewed systematically at 6-month intervals, by an independent Data Monitoring Committee (DMC). There have been no changes to the study design or conduct required based on DMC reviews. Accumulating adverse reaction information from Study COR-2012-01, as described in the IB, is consistent with the safety profile gathered during the investigational use of levoketoconazole in patients with type 2 diabetes.

This proposed OLE study will be limited to subjects who have already demonstrated tolerability to levoketoconazole. Cortendo will provide levoketoconazole only to subjects who have: completed Study COR-2012-01 (defined as those who complete the Extended Evaluation Phase) or Study COR-2017-01 (defined as those who complete the Restoration Phase; or who are rescued early with levoketoconazole); or who subsequently joined a named patient program or other Expanded Access Program; or who were receiving treatment in Study COR-2017-01 in the Dose Titration and Maintenance Phase when randomization to the double-blind Withdrawal Phase was closed. Therefore, all potentially eligible subjects will have been prior users of levoketoconazole. Many subjects will have had experience using a prior-established safe and effective Therapeutic Dose (most will have been levoketoconazole users for over 1 year at time of entry **into the current study**). Certain subjects that were enrolled in Study COR-2017-01 when randomization was closed or subjects with a gap in treatment with levoketoconazole may require re-establishment or establishment of a Therapeutic Dose. As a result, dose titration may be required as outlined in Section 8.2.

2 OBJECTIVES

The objective of this study is to assess long-term safety and efficacy durability of levoketoconazole as chronic treatment for endogenous CS.

3 ENDPOINTS

3.1 Criteria for Evaluation

When calculating changes from Baseline for efficacy evaluations, Baseline will be either or both of:

- Open-label extension (OLE) study Baseline;
- The original parent study COR-2012-01 [SONICS] or COR-2017-01 [LOGICS] Baseline;

with the choice of Baseline described in the Statistical Analysis Plan for each endpoint analysis.

Exploratory Efficacy Endpoints

- Proportions of subjects with mean urinary free cortisol (mUFC): 1) Less or equal to the upper limit of normal (ULN) of the reference range; 2) Above the ULN to 1.5X the ULN; and 3) Above 1.5X the ULN;
- Changes from Baseline in markers of cortisol including mUFC and late night salivary cortisol (LNSC);
- Proportion of subjects with LNSC above the ULN of the reference range;
- Changes from Baseline in Clinical Signs and Symptoms of CS, health-related quality of life (QoL), and symptoms of depression;
- Changes from Baseline in biomarkers of CS comorbidities (fasting blood glucose [FBG], fasting insulin, homeostatic model assessment-insulin resistance [HOMA-IR], hemoglobin A1c [HbA1c], blood pressure, total cholesterol, high-density

lipoprotein-cholesterol [HDL-C], low-density lipoprotein-cholesterol [LDL-C], high-sensitivity C-reactive protein [hsCRP]);

- Frequency of usage and changes from Baseline in frequency of usage of anti-diabetic, anti-cholesterol and anti-hypertensive therapies;
- Compliance (adherence) and persistence with therapy per tablet counts.

3.2 Safety Endpoints

Safety will be assessed by incidence and severity of Adverse Events (AEs), Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESIs) as well as by physical examinations, safety laboratory panels (including Adrenocorticotropic Hormone [ACTH], liver function tests [LFTs], blood chemistry, hematology), electrocardiograms (ECGs) (to include assessment of the QTc interval), vital signs and pituitary Magnetic Resonance Imaging (MRI) for subjects with history of a pituitary tumor.

4 STUDY DESIGN

4.1 Overall Design and Plan

This is a long-term, OLE study of levoketoconazole in subjects with endogenous CS who have completed one or both parent studies or otherwise potentially qualify for this study, as defined in the Inclusion Criteria (Section 5.1):

For subjects entering directly from parent studies, the visit schedule for this OLE study is designed to overlap with those of the parent studies to ensure a smooth transition to the OLE study with no break in drug supply for subjects as shown below.

Extension Study COR-2017-OLE Visit	Screening	Baseline
Can overlap with	⇩	⇩
Parent Study COR-2012-01 (SONICS) visit:	Month 9 (M9)	Month 12 (M12)
Parent Study COR-2017-01(LOGICS) visit:	Restoration Phase Visit 1 (RES1)	Restoration Phase Visit 2 (RES2)

Subjects will remain on the previously established Therapeutic Dose of levoketoconazole that they were last receiving prior to entry in this OLE study.

The study comprises Screening and Baseline Visits followed by visits every 3 months. Dose Adjustment/Safety Monitoring Visits will also be conducted in the event of a need for a dose increase of levoketoconazole during the study.

Details of study assessments and procedures are provided in Section 6. Details of AE monitoring are available in Section 13.5. The timings of assessments are shown in the Time and Events Table (Appendix A).

Adequate medical coverage will be provided by the Investigator continuously during the study (including nights, weekends and holidays) to ensure that prompt safety decisions can be made and appropriate medical interventions provided. The Investigator should

provide all subjects with instructions how to access the medical staff regardless of day and time to obtain medical care.

4.2 Rationale for Study Design

The chosen design has taken into consideration the reported experience treating subjects with CS with ketoconazole [Castinetti et al., 2014]. Like ketoconazole, dosing of levoketoconazole needs to be individualized, since therapeutic need varies considerably among subjects. As such, entry into the study is limited to subjects who have established a safe, tolerated and effective Therapeutic Dose of levoketoconazole in one of the two parent studies.

Long-term safety and tolerability data will be collected at 3-month intervals, with efficacy measures also regularly assessed. Details of safety and efficacy data collection and reporting in this study are provided in Section 6.

If needed, dose increases of levoketoconazole are associated with enhanced monitoring and reporting requirements as summarized in Section 6.1.6. Dose increases must be approved by the Medical Monitor, and should not exceed 150 mg/day, and the dose should not be increased more frequently than every 2 weeks.

Any SAEs and AESIs (i.e. adrenal insufficiency, persistent QT prolongation and potential hepatic events) require reporting within 24 hours as outlined in Section 13.7. All AEs, SAEs and AESIs are anticipated to be reported spontaneously, with inquiries by participating sites at least every 3 months at the clinic visits.

4.3 Study Duration

There is no predefined completion timeframe for this OLE study, and interim analyses may be performed at the Sponsor's discretion. Subjects may continue receiving or discontinue levoketoconazole based on the medical judgement of the Investigator while the study remains open. It is anticipated that subjects' participation may continue for at least 3 years.

5 SUBJECT SELECTION CRITERIA

The Sponsor will review each subject's enrollment criteria to ensure that subjects meet the eligibility criteria.

5.1 Inclusion Criteria

To be eligible for participation in this study subjects for whom the investigator believes long-term use of levoketoconazole may be beneficial must meet **ONE** of the following criteria:

1. Completed the Extended Evaluation Phase of Study COR-2012-01 (i.e. M12).
2. Completed the Restoration Phase of Study COR-2017-01 (i.e. RES2).
   NOTE: Subjects meeting criteria 1 or 2 above who have had a break in therapy may be eligible only after discussion with the Medical Monitor. If eligible, such

subjects may require re-establishment of the Therapeutic Dose via titration. All subjects who have had a break in therapy should be discussed with the Medical Monitor to determine the starting dose of levoketoconazole. Prior to resuming treatment with levoketoconazole, other therapies for Cushing's syndrome must undergo an appropriate washout period, with minimum durations as follows:

- Ketoconazole or metyrapone: 2 weeks;
- Dopamine agonists: bromocriptine (2 weeks), cabergoline (8 weeks);
- Octreotide acetate LAR, lanreotide Autogel®, pasireotide LAR: 12 weeks;
- Lanreotide SR: 8 weeks;
- Octreotide acetate (immediate release) or short-acting pasireotide: 1 week;
- Mifepristone (RU 486, KORLYM®): 4 weeks;
- Megestrol acetate or medroxyprogesterone acetate (and selected other synthetic progestins): 6 weeks.

3. Currently in a named patient program or other Expanded Access Program receiving levoketoconazole.
4. Were levoketoconazole-naïve prior to entry and received early rescue therapy with open-label levoketoconazole in Study COR-2017-01.
5. Achieved a clinically meaningful partial response (with reduction in UFC) in Study COR-2017-01 at dose level 7 or at a maximally tolerated dose of levoketoconazole but did not meet the randomization criteria for Study COR-2017-01 at the end of the Dose Titration and Maintenance Phase when randomization was open.
6. Were levoketoconazole-naïve prior to entry and were enrolled in Study COR-2017-01 in the Dose Titration and Maintenance Phase when randomization was closed. (**NOTE**: Such subjects must receive at least 1 dose of levoketoconazole before transitioning to this study.)

In addition, subjects must meet **ALL** the following criteria:

1. Willing to participate and able to provide written informed consent prior to any study procedures being performed; eligible subjects must be able to understand the informed consent form prior to inclusion into the study.
2. A female is eligible to enter and participate in the study if she is:

    - Postmenopausal, defined as age 50 years or older with amenorrhea for more than 1 year or any age with serum follicle stimulating hormone (FSH) at least 23 mIU/mL and estradiol no more than 40 pg/mL (140 pmol/L) (NOTE: laboratory values obtained during COR-2012-01 or COR-2017-01 protocol will be utilized).

      OR

- Surgically sterile with documented hysterectomy and/or bilateral oophorectomy or tubal ligation.

  OR

- Of child-bearing potential and agrees to use a highly effective method of birth control, as defined in Section 7.1 of this protocol, while participating in the study and for 30 days after the last dose of levoketoconazole. Abstinence is considered acceptable birth control if routinely practiced.

Fertile men must also agree to use a highly effective method of birth control, as defined in Section 7.1 of this protocol, while participating in the study and for 90 days after the last dose of levoketoconazole. Abstinence is considered acceptable birth control if routinely practiced.

3. Able to comprehend and comply with procedures.

5.2 Exclusion Criteria

Subjects will not be eligible for participation in the study if **ANY** of the following criteria are met:

1. Discontinued levoketoconazole while participating in Study COR-2012-01 or Study COR-2017-01 or a named patient program or other Expanded Access program, due to safety or tolerability concerns or lack of efficacy.
2. Pregnant, lactating or intend to conceive while receiving levoketoconazole.
3. Have a medical condition or other circumstances that, in the opinion of the Investigator, might interfere with the subject's participation or pose unacceptable risk to the subject.
4. Scheduled for surgical for treatment of CS or received surgical treatment of CS within the 6 weeks prior to Screening.
5. Had non-CS major surgery within 4 weeks prior to Screening.
6. Treated with mitotane within 6 months prior to enrollment.
7. History of malignancy, including adrenal or pituitary carcinomas (other than low-risk, well-differentiated carcinomas of thyroid, breast or prostate that are very unlikely to require further treatment in the opinion of the treating physician, or squamous cell or basal cell carcinoma of the skin).
8. QTc interval greater than 470 msec via central-reader interpretation during Screening.
9. Clinically significant abnormality in 12-lead electrocardiogram (ECG) during the Screening requiring medical intervention (may be eligible once stable, to be determine case by case).
10. Clinical or radiological signs of compression of the optic chiasm newly apparent since enrolling in a parent study.
11. Liver safety tests during the Screening Phase as follows:

- ALT and/or AST above 3X ULN (NOTE: transaminase values up to 5X ULN may be allowed on an exceptional basis for subjects who have exhibited stable values for at least 3 months)
- AP or TBN above 2X ULN.

Subjects with isolated indirect TBN up to 3X ULN that are presumed to have Gilbert's syndrome may be enrolled if all other liver safety tests are within normal levels.

12. Decreased renal function as defined by eGFR below 40 mL/min/1.73 m^2, using MDRD equation for eGFR.
13. Serum potassium below 3.9 mEq/L (may be supplemented to achieve 3.9 mEq/L or above).
14. Abnormal free thyroxine (FT4), unless subsequently corrected and stable for at least 4 weeks. Subjects with thyroid stimulating hormone (TSH) less than the lower limit of normal (LLN) and normal FT4 are potentially eligible without intervention.
15. Abused alcohol or drugs since enrolling in a parent study (in the Investigator's opinion).
16. Currently participating in another study or has received any investigational treatment (drug, biological agent or device) other than levoketoconazole, within prior 30 days of the Screening visit or five half-lives of treatment, whichever is longer.
17. Current use of any H2-receptor antagonists, proton-pump inhibitors, or sucralfate (all inhibit absorption of levoketoconazole; subjects may be allowed to enroll after washout). [NOTE: A list of acceptable oral antacids will be provided; if used, antacids must be ingested at least 2 hours **after** dosing of levoketoconazole.]
18. Current use of any prohibited concomitant medication that cannot be discontinued safely and washed out completely prior to the Baseline Visit, including but not limited to the following (a more complete list is included in Appendix I):
    - Drugs used to treat Cushing's Syndrome;
    - Weight loss medications (prescription or over the counter);
    - Acetaminophen (paracetamol) above 2 g total daily dose;
    - Strong **inducers or inhibitors** of CYP3A4 enzyme system that may interfere with the metabolism of levoketoconazole and cannot be discontinued prior to first dose;
    - Herbal preparations: St John's Wort, echinacea, gingko, goldenseal, yohimbe, red yeast rice, danshen, Silybum marianum, Asian ginseng, Schissandra sphenanthera, shankhapushpi, and Asian herb mixture (Xiao chai hu tang and Saiboku-to);
    - Topical or inhaled corticosteroids (other than low potency products to be discussed with Medical Monitor first);
    - Carbamazepine;

- Drugs that pose unacceptable risk due to overlapping or exaggerated toxicities or pharmacological action due to presumed PK or pharmacodynamic interactions with levoketoconazole.

6 STUDY ASSESSMENTS AND PROCEDURES

All subjects must meet all inclusion criteria and none of the exclusion criteria prior to OLE study entry. A screen failure occurs when a signed informed consent is obtained but a subject fails to meet some or all eligibility criteria at the OLE Baseline or Screening Visits (if an exclusion criterion cannot be removed or an inclusion principle cannot be met).

The exact timings of each assessment are provided in Appendix A. Detailed procedures are provided in the study manuals.

Throughout the study, subjects should be monitored and managed by the Investigator for diseases or conditions associated with CS or its treatment, per recommended guidelines for diagnosis and standard of care (refer to Appendix J for additional details on conditions potentially associated with levoketoconazole administration).

All medical care providers identified by the subject, in addition to the Investigator, MUST be given sufficient written instructions about the potential risks of adrenal insufficiency associated with the use of cortisol synthesis inhibitors, such as levoketoconazole. Such written instructions will be provided to Investigators for distribution to other medical care providers.

In addition to the protocol-specified procedures, at any time during the study appropriate medical evaluations and safety interventions should be implemented, as necessary, based on the clinical presentation of the subject per standard of care, at the discretion of the Investigator. Changes to the medical conditions, history and medications and all other medical interventions will be documented in the Electronic Case Report Forms (eCRFs).

6.1 Summary of Procedures by Visit

The visit schedule for this OLE study may overlap with those of the parent studies. This is to ensure a smooth transition to the OLE study and no break in drug supply for subjects transitioning from a parent study. Appendix A indicates the procedures and assessments that are required for each of the OLE study visits, including those overlapping with a parent study. Data collected from parent studies will be used in this OLE study and assessments that overlap should be performed once (e.g. data from vital signs may be recorded in an eCRF for the parent study and in an eCRF for this OLE study).

Subjects who have completed a parent study and are currently receiving drug in a named patient program (or equivalent study e.g., individual subject IND) or other Expanded Access Program and are to be rolled over into this OLE study will also follow the visit schedule outlined below and in Appendix A.

6.1.1 OLE Screening Visit

In addition to scheduled assessments conducted for the parent study (i.e., Visit M9 for Study COR-2012-01 or Visit RES1 for Study COR-2017-01) when there is an overlap of parent and OLE study visits, the following assessments will be performed at Screening for enrollment into this OLE study:

- Informed consent: prior to any study procedures, all subjects must understand and sign the informed consent.
- Review and confirmation of eligibility (inclusion/exclusion criteria). **NOTE:** Assessments from the parent study will also be used to support eligibility assessment for this OLE study.

For subjects whose parent study visits align with the OLE Screening and/or Baseline, Appendix A does not account for additional tests required as part of Study COR-2012-01 or Study COR-2017-01. Refer to the parent study's respective Time and Events Schedule to ensure all required tests are completed. Subjects from an Expanded Access Program will have all tests conducted per Appendix A.

In some cases, subjects may have a gap between completing a parent study and enrolling in this study that may in some cases involve a break in treatment. For subjects who have completed a parent study within 6 months, the Screening Phase will rely primarily on data collected during the parent study and completed with data collected in OPTICS. In order for the Screening and Baseline visit to be combined, the ECG, LNSCs and LFTs must be obtained within 2 weeks of the Screening/Baseline visit and UFCs must be obtained within 6 weeks of the Screening/Baseline visit.

Subjects entering this study following a break in therapy of **greater than or equal to six months** will undergo all Screening and Baseline procedures as outlined in Appendix A.

6.1.2 OLE Baseline Visit

The Baseline Visit for the OLE study will usually occur on the same calendar day as the last treatment visit of the parent study (Appendix A). This visit will include a final assessment of subject qualifications for this OLE study, prior to treatment being dispensed. Subjects from an Expanded Access Program will have all assessments conducted per Appendix A.

In addition to the scheduled assessments being conducted for the parent study at either M12 or RES2 (depending on the corresponding parent study), the following assessments will be performed at the Baseline Visit:

- Reconfirm no changes in eligibility (inclusion/exclusion criteria) from OLE Screening Visit. **NOTE:** Assessments from the **parent study** will also be used to support eligibility assessment for this OLE study.
- Fasting insulin and hsCRP (For COR-2012-01 subjects only, as these assessments are not included in M12).

For subjects whose parent study visits align with OLE Screening and/or Baseline, Appendix A does not account for additional tests that need to be collected as part of Studies COR-2012-01 and COR-2017-01. Refer to the parent study's respective Time and Events Schedule to ensure all required tests are completed. Also, for those assessments overlapping between the parent study's corresponding visit to OLE Screen and/or Baseline the parent study's material will be used. Assessments not overlapping will be conducted using the materials from COR-2017-OLE.

After eligibility is confirmed and the assessments shown in Appendix A are recorded, levoketoconazole will be dispensed for continued use.

NOTE: ECGs from the parent study will occur prior to taking the morning dose of levoketoconazole. Following the first dose of drug in this study, another ECG will be performed 1-2 hours later.

6.1.3 Regular Study Visits

Regular visits are to occur every 3 months (+/- 7 days), or more often as necessary for enhanced safety monitoring (e.g. if a dose increase is required). Some procedures, however, are required only every 6 months, and MRIs are required annually and only for subjects with history of a pituitary tumor. The timings of each assessment are shown in Appendix A.

6.1.4 Final Study Visit

At a subject's Final Study Visit, all procedures that occur every 3 months, every 6 months, and annually, will be performed (as shown in Appendix A).

6.1.5 Follow-up Call

One week following the Final Study Visit, subjects will be contacted via telephone by the Investigator or designee. The subject will be asked about any changes in their health since the Final Study Visit.

6.1.6 Dose Adjustment/Safety Monitoring Visits

In the event of a need for a dose increase of levoketoconazole during the study, regardless of dose level or prior treatment at that dose level, additional safety monitoring, as described in Table 1 and in Appendix A, is required in addition to all other assessments listed in Appendix A under Dose Adjustment/Safety Visits.

NOTE: Doses should <u>not</u> be increased without permission of the Medical Monitor. Dose increases **should not exceed 150 mg/day** and the dose should not be increased more frequently than every 2 weeks. A careful history should be obtained to **look for a precipitant of apparently decreased drug effectiveness** (e.g. use of concomitant medication that interferes with levoketoconazole absorption).

Table 1 Dose Adjustments/Safety Monitoring Assessments and Timing Following Dose Increase

	Any Dose Increase
LFTs (AST, ALT, GGT, AP, LDH and total and direct bilirubin)	Biweekly for 1 month (twice in total) unless total daily dose is greater than 600 mg, then weekly (4 times for 1 month)
12-lead ECG - To check for evidence of QTc prolongation	1 to 2 hours after dosing at the new (higher) dose and again after 1 month
Cortisol monitoring (e.g. UFCs, Serum Cortisol, Salivary Cortisol)	Biweekly for 1 month (twice in total)

Dose interruptions or decreases are allowed at any time the discretion of the Investigator without prior consultation in cases of intolerability or adverse effects, including excessive cortisol reduction (i.e. adrenal insufficiency) and will be reported to the Medical Monitor as soon as possible.

A decrease of levoketoconazole requires additional reporting if it occurs as a reaction to an AESI associated with the use of levoketoconazole.

6.2 Study Assessments

6.2.1 Physical Examination and Assessment of Clinical Signs and Symptoms of CS

Full physical examinations will be performed by a study physician or designee (e.g. a nurse practitioner or physician's assistant) at the times indicated in Appendix A. The physical examinations will be inclusive of all body systems (except genitourinary and rectal) and should include height (cm) and weight (kg). Body mass index will be derived based on data entered in the eCRF during the visit.

At some visits, the examining physician will be asked to complete a questionnaire related to the assessment of Clinical Signs and Symptoms of CS (see Appendix L). The results will be used to quantify changes in Clinical Signs and Symptoms of CS.

6.2.2 Vital Signs

Vital sign measurements will include temperature, sitting systolic blood pressure (SBP), sitting diastolic blood pressure (DBP) and heart rate (HR) at the OLE Baseline Visit and at each subsequent visit throughout the study (see Appendix A). Blood pressure and HR will be done in triplicate at each visit.

For proper measurement of blood pressure, the following procedures should be followed:

- An appropriately sized cuff for the size of the subject's arm circumference should be used to minimize inaccurate readings;
- Subjects should not smoke or exercise for at least 30 minutes before blood pressure measurements;
- Subjects should sit in a chair with a back support and the arm supported at heart level with feet flat on the floor;

- Subjects should void prior to the measurement and;
- Blood pressure measurements will be made in triplicate over a minimum of approximately 10 minutes after the subject has rested in a sitting position for at least 10 minutes. The three measurements will be recorded individually in the eCRF and a mean value for that visit calculated.

Vital sign measurements must be repeated if reported as clinically significant or if machine/equipment errors occur. Not clinically significant, out-of-range blood pressure or HR measurements may be repeated at the Investigator's discretion. Any confirmed, clinically significant adverse change from the OLE Baseline in vital signs must be recorded as an AE.

Guidelines for classification of blood pressure readings and recommendations for follow-up of abnormal values are provided in Appendix H.

6.2.3 Spaulding 12-Lead Electrocardiograms (ECG)

QTc interval prolongation is considered an important identified risk of levoketoconazole therapy (as discussed in the IB). The mechanisms by which levoketoconazole may prolong the QTc interval are multiple and may include: direct hERG (IKr potassium channel) inhibition (observed in vitro), interference with metabolism of drugs that prolong the QTc (observed in vitro and in clinical studies), changes in adrenal hormone levels that lead to hypokalemia (theoretical) and induction of nausea (observed in clinical studies).

The QTc interval is highly variable and readily influenced by exogenous factors. For examples, food intake increases the QTc interval. Nausea, vomiting, upset stomach, dizziness and electrolyte abnormalities (especially relevant to this study, **hypokalemia**/hypomagnesemia) can also prolong the QTc interval. Such factors should be avoided when possible (e.g. electrolytes should be replaced as needed to maintain serum levels well within the normal range) during QTc measurements and should be considered when interpreting QTc interval findings.

In this study, ECG monitoring is being performed at the designated times shown in Appendix A using a Spaulding ECG device that acquires a 12-lead ECG continuously over a pre-programmed period (minimum time of 1 minute to maximum time of 5 minutes). A summary of the ECG assessment will be generated via central reading by Spaulding, with the results serving as the definitive measurement of QTc. Additionally, the Spaulding device will provide a real-time automated analysis (using the University of Glasgow diagnostic 12-lead algorithm, [Macfarlane 2005]) of the ECG that can serve as an unconfirmed measurement of QTc interval for purposes of safety monitoring.

NOTE: The Spaulding ECG device should be used for all assessments during the study unless it is non-operational, in which case another ECG may be performed on a local device or a device other than the Spaulding device supplied for this study and transmitted to Spaulding for central reading via printout. A 12-lead ECG will be obtained within approximately 1 to 2 hours after drug administration (i.e., at approximately the peak plasma concentration of levoketoconazole) after the subject has rested in a supine position for at least 5 minutes and after the subject has not eaten for at least 2 hours (small snacks may be allowed for subjects with diabetes).

In general, QTc interval measurements are considered "normal" or "abnormal prolonged (clinically significant)" or "abnormal prolonged (not clinically significant)". If the QTc results have been identified as "abnormal prolonged", whether it is deemed clinically significant or not, these results should be reported to the Sponsor's designated safety group as an AESI (Section 14.1.1 and 14.1.2), appropriate action taken and the event recorded in the eCRF. Other than the AESI for QTc interval prolongation, there is no additional formal reporting of ECG findings required for this study; however, clinically significant findings other than QTc prolongation should be reported as an AE, SAE or AESI, as applicable per definitions in Section13.5 and 14.

NOTE: For subjects entering directly from Study COR-2012-01, the Spaulding device previously used in the parent study is not planned for use in this OLE study. However, it is acceptable to use the prior device for the OLE Screening and/or Baseline Visit.

Additional information for assessment of QTc interval is available in Appendix N.

6.2.3.1 Procedures for Evaluating and Managing Prolonged QTc Interval Greater than 500 Msec or More than 60 Msec Above Baseline

If at any time during the study, the Spaulding automated ECG reading indicates a QTc interval greater than 60 msec above Baseline or an absolute QTc interval more than 500 msec:

- The other ECG findings and the subject's clinical condition must be considered to determine the plan of action. QTc prolongation that is accompanied by Torsades de Pointes, polymorphic ventricular tachycardia, or ECG abnormalities accompanied by clinical signs/symptoms of serious arrhythmia might require urgent intervention and inpatient monitoring; immediate cardiology consultation is recommended.
- With one abnormal ECG reading, the subject **should first be questioned** about:
  - Recent ingestion of food within the preceding 2 hours. If the subject has eaten, a repeat ECG evaluation should be conducted following a proper 2-hour fast and rest.
  - The use of any other medications that may have increased QTc interval, either directly (via direct effect on the QTc interval) or indirectly because of a drug interaction that may have increased the concentrations of study medication (see Appendix I). If such a drug is identified, it should be stopped immediately.
  - Symptoms of nausea or vomiting just prior to the ECG assessment, or lightheadedness or similar symptoms that may influence the QTc interval. In such cases, an ECG evaluation should be repeated once the subject's symptoms have abated. Study medication may have to be withheld if the symptoms are protracted and the QTc interval prolongation remains evident. The Investigator should ensure that the symptoms as well as the ECG results are not due to a cardiovascular event, such as a myocardial infarction.

- If the subject has not eaten, has no confounding medical symptoms/events, does not have a concomitant medication that may be increasing the QTc interval, and there are no other significant abnormalities on the ECG warranting immediate medical intervention then:
  - A repeat ECG evaluation should be undertaken within approximately 30 minutes of the observed ECG prolongation or as soon as it is practical.
- If the repeat ECG evaluation continues to demonstrate a QTc interval more than 60 msec above Baseline or an absolute value more than 500 msec, blood samples should be obtained from the subject for evaluation of electrolyte abnormalities, including at a minimum magnesium, calcium and potassium.
  - If electrolyte abnormalities are subsequently identified, these should be corrected before re-evaluation of the ECG. Study medication may be temporarily withheld until electrolytes can be normalized. It is recommended to keep serum potassium concentration in the high-normal range (i.e. 4 mEq/L or higher).
  - If electrolytes are normal and no other cause can be identified to account for the absolute QTc interval above 500 msec, and the ECG evaluation on repeat determination demonstrates persistent QTc prolongation, a causal relationship to study medication should be assumed and study medication should be withheld. If the ECG is otherwise benign, the ECG should be monitored approximately once per week until resolution of the QTc prolongation or until another etiology is identified if the QTc prolongation does not correct.
- In all cases, abnormal morphology of the ECG (especially T wave changes), if present, should be considered an AE and be recorded in the eCRF.

6.2.4 Clinical Laboratory Tests

Clinical laboratory testing should, at a minimum, be conducted at the times indicated in Appendix A. As noted in Section 6.1.6, subjects require more frequent (biweekly or weekly) monitoring of liver function in the month following an increase in dose during the OLE study. Clinically significant changes in laboratory analyte values should be reported as an AE, SAE or AESI, as applicable per definitions in Section 14.

A complete list of all the analytes is provided in Appendix B.

All testing will be conducted in the morning following a 12-hour fast (small snacks may be allowed for subjects with diabetes; any food intake should be recorded in the subject source documents for reference) unless indicated otherwise in the laboratory manual.

Routinely scheduled laboratory tests will be assayed at the study's central laboratory.

6.2.5 Disease-Related Assessments

Cortisol will be routinely assessed throughout the study.

Cortisol assessments will be used to monitor durability of the therapeutic effect of levoketoconazole and for evidence that might suggest increased risk of adrenal

insufficiency. If the clinical status requires a dose increase of levoketoconazole, cortisol levels should be monitored biweekly for 1 month (Section 6.1.6).

NOTE: The clinical diagnosis of adrenal insufficiency (for which guidance is provided in Section 14.3 should be reported as an AESI.

6.2.5.1 24-Hour UFC

24-hour urine collections for determination of UFC are needed for drawing reliable efficacy inferences from this study. Subjects should be fully informed prior to initiating procedures that they will be asked to collect 24-hour urine samples at regular intervals throughout the study, possibly including during work days and holidays.

Please see the SPM and the Laboratory Manual for details on urine collection procedures. Note that, lifestyle and dietary restrictions listed in Section 7 state subjects should be instructed to avoid consuming more than 4 L/day of liquids on the day of urine collections.

Urine will be collected in provided containers. The parent study's materials will be used for all tests that overlap with this OLE study. Three adequate 24-hour urine collections for UFC will occur at every visit indicated in Appendix A, except if subject's OLE Baseline Visit overlaps with M12 (as part of COR-2012-01), then 2 collections will be collected. The total volume of urine and urine creatinine excretion rates will be measured from the 24-hour collections as markers of collection adequacy, as detailed below in this section. Collections judged to be inadequate should be repeated; the rationale for repeat collections should be captured in the eCRFs.

Urine collections will ideally begin enough in advance of a visit to allow discussion of the results at the visit (i.e. usually 7-14 days prior) if being delivered by courier. Collections can also be delivered by the subject between visits personally. Careful instructions must be provided to the subject for proper urine collection and cold-storage of samples until delivery. All supplies (i.e. waterproof pen, urine jugs, urine hats and labels) needed for proper collection and storage of urine will be provided by the Sponsor or its laboratory vendor to Investigators for distribution to subjects.

Determining urine collection adequacy

The total volume of urine and urine creatinine excretion rate will be measured from 24-hour collections as markers of the adequacy of collection. Total urine volume should

be between 400 and 4000 mL/day. Expected values for normal 24-hour creatinine excretion rates for subjects up to age 70 years are provided in **Table 2**.

Table 2 Expected Normal 24-Hour Creatinine Excretion from Adequate Urine Collections

Males	1. Age 18 to 50: 18.5 mg/kg/day 2. Age 51 to 70: 15.7 mg/kg/day
Females	1. Age 18 to 50: 16.5 mg/kg/day 2. Age 51 to 70: 11.8 mg/kg/day
In subjects over 70 years of age, creatinine excretion rates should be discussed on a case by case basis with the Medical Monitor.	

Note that the above values were derived from populations of generally healthy individuals without kidney dysfunction. Due to the muscle wasting observed in CS and dependent on the length of the disease, subjects may have 24-hour urine creatinine excretion rates below the values reported in **Table 2** [Petersenn 2013]. Therefore, creatinine excretion values that are somewhat below the normative value will be considered indicative of adequate collection when urine volume is adequate. The Medical Monitor will provide guidance as to the adequacy of the collection.

Urinary Free Cortisol Sample Analysis

UFC levels from the 24-hour urine collections will be assayed at a central laboratory per validated methodology using high pressure liquid chromatography tandem mass spectroscopy.

6.2.5.2 Collection of Late Night Salivary Samples for Free Cortisol

LNSC samples from 2 nights will be collected by each subject at the times indicated in Appendix A. Saliva collections must be done between 11 PM and midnight and following the dietary restrictions listed in Section 7. Subjects should not sleep and subsequently awaken within 2 hours of collecting the saliva sample.

All samples will be analyzed at a central laboratory. Details for collection and handling of samples are provided in the SPM and laboratory manual.

6.2.5.3 Morning Cortisol and Adrenocorticotrophic Hormone (ACTH)

Morning serum cortisol (untimed) will be measured in all subjects every 3 months and at Dose Adjustment/Safety Monitoring Visits in the event of a need for a dose increase of levoketoconazole during the study. ACTH levels will be measured in all subjects every 6 months and at Dose Adjustment/Safety Monitoring Visits, as listed in Appendix A.

6.2.5.4 Pituitary Magnetic Resonance Imaging (MRI) For Subjects with History of a Pituitary Tumor, Such as Cushing's Disease [CD], Only

Pituitary MRIs will be obtained for all subjects with history of a pituitary tumor, including those with CD, at the OLE Baseline Visit (if not previously done within the last 6 months). The scheduled interval between MRIs should be one every 12 (± 2) months. The main purpose is to assess tumor size, which will be measured by a central neuroradiologist.

6.2.5.5 Subject Diary

Subjects will be asked to maintain a patient diary to record medication administration, urine sample collection, saliva sample collection, concomitant medications, and changes in condition. Subjects will be instructed to bring the completed diary to each regular study visit at which time a new diary will be dispensed.

6.2.5.6 Quality of Life and Psychometric Assessments

The Cushing QoL questionnaire [Webb 2008] [Appendix K] and the Beck Depression Inventory (BDI-II) [Appendix M] instrument will be administered at the times indicated in Appendix A.

6.2.6 Situations Requiring Additional Safety Monitoring

Additional safety monitoring will be required for AESIs outlined in Section 14. The list is not intended to be an all-inclusive list of situations that could prompt additional safety monitoring.

Dose Increases

If a dose increase is required, additional safety monitoring is required (Section 6.1.6).

Dose increases (regardless of dose level or prior treatment at the higher dose level) should be reported on the eCRF along with the rationale for dose increase.

6.3 Additional Considerations for Risk Management

6.3.1 Instructions for Subjects

Subjects will be instructed to carry a card or other identifier (e.g. bracelet or pendant) always that clearly indicates the potential risk for adrenal insufficiency. This card will include the subject's information, contact information for the Investigator, and the potential need for glucocorticoids in cases of shock, surgery, and other conditions, as appropriate.

Subjects should be regularly apprised of the potential risk for adrenal insufficiency and be made aware of the signs and symptoms of this condition. At any time during the study, subjects should contact the clinical site in the event of any emerging clinical signs and symptoms of an AE. Clear instructions should be provided to the subject on how to access the medical staff at the investigational site regardless of day or time of day.

In addition, subjects will also be asked to carry an emergency kit containing hydrocortisone or another appropriate glucocorticoid, **per local medical practice**, that can be administered immediately in case of adrenal insufficiency. Subjects must be instructed on the proper use of the emergency glucocorticoid.

6.3.2 Considerations for Investigator

Throughout the study, subjects must be monitored and managed by the Investigator for the following conditions associated with CS or its treatment, per prevailing guidelines for diagnosis and standards of care:

- Diabetes and impaired glucose tolerance: See Appendix G for testing recommendations.
- Hypertension: See Appendix H for guidelines for classification of blood pressure levels and follow-up recommendations.
- Hypocortisolemia: See Appendix J for evaluations of signs and symptoms.
- Hypomineralocorticoidism: See Appendix J for evaluations of signs and symptoms.
- Hypogonadism: See Appendix J for evaluations of changes in sexual function as reported by the subject.
- Acute adrenal crisis: Acute adrenal crisis **is a life-threatening condition** that often occurs primarily because of mineralocorticoid deficiency (Appendix J). In such cases, the major clinical problem is hypotension (low blood pressure or shock). Adrenal crisis can result in seizures, shock, coma or death. In patients treated for CS, adrenal crisis typically occurs in the setting of acute stress or pituitary infarction. With pituitary infarction, glucocorticoid deficiency can predominate. Note that levoketoconazole per se is **not** anticipated to incite acute adrenal crisis as mineralocorticoid production is not anticipated to be affected to a clinically meaningful extent.
- Adrenal insufficiency: See Section 14.3 for management of adrenal insufficiency.

7 LIFESTYLE AND DIETARY RESTRICTIONS

Subjects must follow these lifestyle and dietary restrictions throughout the study.

- Levoketoconazole should usually be taken at approximately the same times each day, and for the most consistent day-to-day absorption, should be ingested with the same types of liquids and/or foods each day (see Section 8.2).
- Consumption of grapefruit, lime juice and Seville oranges (aka sour orange, bigarade orange, or marmalade orange) and its products should be limited to once weekly owing to potential drug interactions with levoketoconazole that may influence its bioavailability;

- Genuine licorice (not the same as licorice-flavored candy) should be limited to once weekly due to its mineralocorticoid effects;
- Consumption of excessive alcohol should be avoided (note: there is no known safe amount in relation to use of levoketoconazole);
- Subjects should not smoke or exercise for at least 30 minutes before blood pressure measurements; and
- Subjects should not eat for at least 2 hours prior to ECG.

Subjects must follow the following lifestyle and dietary restrictions for study-specific assessments.

- During the **24-hour urine collection** period, subjects **must refrain** from the following:
  - Drinking more than 1 gallon or 4 liters of fluids; and
  - Use of medicines or other products containing corticosteroids, whether administered topically (e.g. drops, creams), inhaled, or ingested.
- On the nights that samples are collected for **LNSC**, subjects **must refrain** from the following:
  - Within **2 hours** prior to the collection:
    - Brushing or flossing teeth or doing anything that could induce bleeding of the gums; and
    - Sleeping and subsequently awakening
  - Within **1 hour** prior to the collection:
    - Eating or drinking or chewing anything (including tobacco);
    - Using any facial creams or lotions; and
    - Smoking cigarettes, pipe, cigar or any other substance.

Information on each subject's sleeping hours will be collected.

7.1 Prevention of Pregnancy

Regardless of menopausal status, all female participants must have a negative pregnancy test at study visits indicated in Appendix A. Urine beta human chorionic gonadotropin (βhCG) will be assayed on site. Definition of postmenopausal is found in the Inclusion Criteria (Section 5.1)

Women of child-bearing potential must agree to use a highly effective method of birth control, as defined below, while participating in the study and for 30 days after last dose of levoketoconazole. Acceptable methods include the following:

- Male partner is sterile prior to female subject entry into the study, and this male partner is the sole partner for that subject; or

- Implant of levonorgestrol inserted for at least 1 month prior to study medication administration but not beyond the third successive year following insertion (must be replaced); or
- Oral contraceptive (combined or progestogen only) administered for at least one monthly cycle prior to study medication administration and throughout the study; or
- Double-barrier method: condom or occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository); or
- An intrauterine device; or
- Estrogenic vaginal ring; or
- Percutaneous contraceptive patches; or
- If medical contraceptives and barrier methods are not feasible for medical or religious reasons, an assurance of abstinence will be deemed an acceptable form of contraception if routinely practiced.

Fertile men must also agree to use a highly effective method of birth control as defined above, while participating in the study and for 90 days after the last dose of levoketoconazole. Abstinence is considered acceptable birth control if routinely practiced.

Reports of pregnancies in female subjects (or in female partners of male subjects) will be collected after the start of dosing and until the Final Study Visit. Female subjects found to be pregnant will be withdrawn from the study.

7.2 Action to be Taken if Pregnancy Occurs

The Investigator will collect pregnancy information on any female subject or a male subject's partner who becomes pregnant while participating in this study. The pregnancy informed consent form (ICF) must be signed if a male subject's female partner becomes pregnant. This ICF is to allow for pregnancy and outcome information to be collected. The Investigator will record pregnancy information on the appropriate form and submit it to the Medical Monitor within 24 hours of learning of the pregnancy. The subject will also be followed to determine the outcome of the pregnancy. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Premature termination of the pregnancy will be reported.

All pregnancies will be reported by the Investigator and documented per the same procedures as SAE. While pregnancy will not be considered an SAE, any pregnancy complication or elective termination of pregnancy for medical reasons will be recorded as an AE or SAE, as indicated.

Spontaneous abortion is always considered an SAE and must be reported as such. Furthermore, any SAE accompanying and related to a post-study pregnancy, which is considered reasonably related to the investigational product by the Investigator, will be reported to the Medical Monitor. However, Investigators are not obligated to seek such information proactively from former study participants.

8 INVESTIGATIONAL PRODUCTS

8.1 Description of Investigational Product

Levoketoconazole will be provided as 150-mg immediate release tablets for oral administration. The tablets will be 3/8" round, biconvex, and unmarked with a pink film coat and supplied in foil induction sealed High-Density Polyethylene bottles. Refer to the Pharmacy Manual for details of labeling of the investigational product.

8.2 Dosage and Administration

Subjects will receive an adequate amount of the investigational product at each visit, starting at the Baseline Visit as prepared by the study pharmacist. Please refer to the Pharmacy Manual for dispensing instructions. Although no specific restrictions are made regarding the ingestion of fluids or food around the time of dosing, it is believed, via inference from studies with ketoconazole, that gastric acidity is needed for absorption of levoketoconazole. Therefore, varying the timing of food intake in relationship to dosing, which can affect gastric acid, or the type of beverage routinely ingested during establishment of the Therapeutic Dose, is not recommended, as doing so might lead to excessive variability in levoketoconazole blood levels and thus a changed response to therapy.

Doses of levoketoconazole can range from a total daily dose of 150 mg up to 1200 mg. Levoketoconazole will be administered daily, approximately every 12 hours, per the individual Therapeutic Dose previously established for each eligible subject during the parent study or as subsequently modified. The minimum daily dose is 150 mg once a day for subjects who cannot tolerate 150 mg twice a day.

Increases of dose are allowed, but only after consultation with and approval by the Medical Monitor, and are accompanied by enhanced safety monitoring, as per the Dose Adjustment/Safety Monitoring Visits in Appendix A and Section 6.1.6. Dose increases should not exceed 150 mg/day per occasion and should occur no more frequently than once every 2 weeks unless first discussed with the Medical Monitor or designee. Dose increases should be recorded on the eCRF. Dose interruptions or decreases are allowed at any time at the discretion of the Investigator without prior consultation in cases of intolerability or adverse effects, including excessive cortisol reduction (i.e. adrenal insufficiency) and will be reported to the Medical Monitor as soon as possible.

For subjects that have had a gap in treatment with levoketoconazole prior to entry in COR-2017-OLE, re-establishment or establishment of a subject's Therapeutic Dose at the baseline visit may be necessary and, as a result, dose titration may be required. Subjects that were in the Dose Titration and Maintenance Phase of Study COR-2017-01 when randomization was closed may also require establishment of a Therapeutic Dose. In both of these instances, the Investigator will consult with the Medical Monitor to determine the starting dose of levoketoconazole. Subsequent dose increases to the subject's previously established Therapeutic Dose or Maximally Tolerated Dose should not exceed 150 mg/day per occasion and should occur no more frequently than once every 2 weeks unless otherwise agreed with the Medical Monitor or designee.

8.3 Blinding

Not applicable.

9 DRUG SUPPLIES, DISPENSING, STORAGE AND ACCOUNTING

9.1 Product Storage

Levoketoconazole should be stored at 20°C to 25°C (68°F to 77°F). Avoid excessive exposure to light or humidity. Records of the actual storage conditions during the period of study must be maintained (i.e. Records of the date, time and initials of the person checking, daily temperature or continuous temperature recordings, or regularly maintained temperature alarm systems used in conjunction with temperature records). Daily temperature monitoring and documentation are required to confirm no temperature excursions have occurred.

9.2 Product Accountability

Levoketoconazole is considered an Investigational Drug Product for purposes of this OLE study, regardless of its marketing approval status. The Investigator is responsible for investigational product accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the Investigator or designated site staff must maintain investigational product accountability records throughout the course of the study. The responsible person(s) will document the amount of investigational product received from Sponsor designee (when applicable), the amount supplied and/or administered to and returned by subjects, if applicable.

9.3 Drug Supply and Resupply

Please refer to the Pharmacy Manual for details of drug supply, dispensing, accountability, reconciliation and destruction or return.

9.4 Compliance Assessment

Subjects should bring all empty medication bottles and unused medication with them to all visits except for additional Dose Adjustment/Safety Monitoring Visits (where empty medication bottles and unused medication will not be collected and accountability will not be performed). Accountability to determine treatment compliance will be performed at all other in-clinic visits.

9.5 Treatment of Investigational Product Overdose

There is no known direct antidote to levoketoconazole once absorbed. However, if a large overdose of levoketoconazole was recently ingested, in addition to maneuvers aimed at removing tablets from the stomach, its absorption from the intestines into blood might be reduced by ingesting fatty foods/liquids.

Subjects should be medically managed based on their clinical condition (e.g. monitor and treat for hypocortisolism).

10 CONCOMITANT MEDICATIONS

10.1 Common Permitted Medications

For management of dyslipidemia, pravastatin, fluvastatin, pitavastatin and rosuvastatin are the only allowed "statins".

For management of hypokalemia, slow-release potassium supplements are encouraged. Maintenance of serum potassium levels within the normal range and above 4.0 mEq/L may reduce the risk of drug-induced QTc prolongation.

Most medications used to treat type 2 diabetes mellitus are allowed. Metformin is allowed, although its levels might be increased by levoketoconazole. Routine monitoring of glucose and kidney and liver function is considered sufficient to mitigate any risk of the combination with levoketoconazole.

For managing dyspepsia, over the counter liquid and tablet antacids containing e.g. aluminum, calcium, or magnesium, are allowed but must be used in moderation and taken at least 2 hours **after** dosing with levoketoconazole. A country-specific list will be provided.

Most commonly used treatments for osteopenia or osteoporosis—excluding certain hormonal treatments—are allowed. Calcium supplements should be taken at least 2 hours **after** ingesting study medication, as they may interfere with levoketoconazole absorption via antacid effects.

All medications should be scrutinized at the OLE Screening Visit, using Appendix I as a guide and with help from the Medical Monitor if needed. Medication additions or switches after the OLE Screening Visit should be kept to a minimum and should likewise prompt a check against Appendix I, ideally prior to the decision to add or switch, to prevent untoward experiences, including loss of efficacy, resulting from drug interactions. Any questions concerning concomitant medications should be addressed with the Medical Monitor promptly.

Blood pressure, diabetes, cholesterol, and CS-specific medications will be captured with other medications but will require Investigator specification of the medication types.

10.2 Prohibited Medications

During the study, subjects are not allowed to take the following medications. A more complete list of prohibited medications and medications to be used with caution, categorized by primary reason for prohibition or precaution, is found in Appendix I. The Investigator is encouraged to contact the Medical Monitor for any questions.

- Total daily dose of acetaminophen (paracetamol) above 2 g (increased liver toxicity risk);
- Prescription or over the counter H2-receptor antagonists or proton-pump inhibitors or sucralfate (inhibition of drug absorption, Appendix I, Table 12;
- Statins other than pravastatin, fluvastatin, pitavastatin and rosuvastatin (Appendix I, Table 13);
- Carbamazepine (Appendix I, Table 14);

- Steroidogenesis inhibitors or dopamine agonists (interference with study drug assessment, Appendix I, Table 7 and Table 8);
- Megestrol acetate or medroxyprogesterone acetate and selected other synthetic progestins (see Appendix I, Table 9) [Schindler 2003];
- Any other drug treatments used to lower cortisol in CS that are subject to washout (Appendix I, Table 10) are prohibited throughout the study;
- Weight loss medications, either prescription or over the counter (Appendix I, Table 11);
- Drugs whose systemic exposure is potentially increased significantly by concomitant use of levoketoconazole (Appendix I, Table 13);
- Drugs that pose unacceptable risk due to overlapping or exaggerated toxicities or pharmacological action due to presumed PK or pharmacodynamic interactions with levoketoconazole (Appendix I).
- Medications that are **strong** CYP3A4 inhibitors or CYP3A4 inducers as they may interfere with the metabolism of levoketoconazole. As examples, rifampicin, rifabutin, isoniazid, nevirapine and phenytoin may significantly reduce levoketoconazole concentrations via CYP3A4 induction, and ritonavir may increase levoketoconazole concentrations via CYP3A4 inhibition, and are therefore prohibited (Appendix I, Table 14);
- Medications resulting in QTc prolongation as a direct effect or as a result of interaction with levoketoconazole, examples include: cisapride, dofetilide, pimozide, and quinidine. (Appendix I, Table 13 and Table 15). However, in selected cases where no alternative medications are available, permission from the Medical Monitor may be sought;
- Topical or inhaled corticosteroid preparations, except for low potency preparations (interference with study drug assessment, Appendix I, Table 17);
- The following herbal medicines: St John's Wort (Appendix I, Table 14), echinacea, gingko, goldenseal, yohimbe, red yeast rice (Appendix I, Table 18), danshen, Silybum marianum, Asian ginseng, Schissandra sphenanthera, shankhapushpi, and Asian herb mixture (Xiao chai hu tang and Saiboku-to);

10.3 Medications to be Used with Caution

There are some medications that are often considered contraindicated when used with ketoconazole due to an increased risk of AEs (Appendix I, Table 18). These medications should generally be avoided while the subject is participating in the study. However, they may be used in selected cases, particularly when they are used prior to study entry and when no alternative medications are available. Such usage should follow consultation with and explicit permission from the Medical Monitor.

Medications that are weak or moderate CYP3A4 inhibitors or CYP3A4 inducers or that are metabolized by cytochrome P450 enzymes (CYPs) and plasma concentration that increase in exposure moderately in the presence of ketoconazole, potentially resulting in increased drug effect, should be avoided if alternative therapy is available or should be used with caution. In such cases, careful monitoring, with possible adjustments in doses, is recommended (see Appendix I, Table 16).

11 SUBJECT COMPLETION AND WITHDRAWAL

11.1 Subject Completion

There is no specific completion timeframe for this OLE study. Subjects may continue receiving or discontinue levoketoconazole based on the medical judgement of the Investigator until the study is closed.

11.2 Subject Withdrawal Criteria and Procedures

Subjects have the right to discontinue participation in the study at any time. Reasons for withdrawal during the study may include, but are not limited, to the following:

- Withdrawal of informed consent or lost to follow-up;
- Safety reasons, as stipulated in Section 13 and 14 either at the discretion of the Investigator or at the subject's request;
- Protocol violations at the discretion of the Sponsor;
- Plan to receive or need concomitant therapy that could interfere with the safety of the subject including, but not limited to use of prohibited medications (Section 10.2 and Appendix I),
- Use of any other medications to treat CS or CD due to the lack of data on the safety of levoketoconazole used in combination with other CS medications, or
- Subjects scheduled for surgery or radiotherapy for treatment of their CS or CD should be withdrawn and such subjects should be transitioned to an alternative medication if necessary.

All study withdrawals and their causes must be documented, to include the specific reason(s) prompting withdrawal, by the Investigator on the eCRF, and, if need be, on the SAE form, AESI form and/or AE eCRF. The reason for withdrawal will be entered in the eCRF.

If the subject chooses to withdraw or is otherwise withdrawn from the study, the Investigator should make every attempt to have the subject return to the clinic to complete safety assessments as outlined for the Final Visit in Appendix A. All data gathered on the subject prior to termination will be made available to the Sponsor.

All safety data pertaining to a causally related AE, SAE or AESI associated with study withdrawal must be provided to the Sponsor. All AEs should be followed until resolution or a minimum of 30 days after the last dose of levoketoconazole.

12 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

12.1 Population for Analysis

Intent-to-treat (ITT) Population: The ITT population will include all subjects who provide informed consent and receive at least one dose of levoketoconazole in this OLE study. This population will be used for the analyses of safety and efficacy.

12.2 Hypothesis

There is no formal hypothesis to be tested in this OLE study.

12.3 Sample Size Determination

Given that this is a single-arm OLE study with exploratory efficacy endpoints only, there is no formal hypothesis to be tested, and the sample size to be enrolled is not pre-determined.

12.4 General Consideration for Data Analysis

The SAS System, Version 9.2 (or higher), will be used for all analyses, unless otherwise specified. Continuous variables (e.g., age) will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables (e.g., sex) will be summarized using the number of observations (n) and percentage in each category.

Data summaries will be presented for all subjects combined and, where appropriate, by dose group (i.e., the previously established Therapeutic Dose that subjects were last receiving prior to entry to this OLE study) as well.

For the purposes of analyzing changes or shifts from Baseline, whether for safety or efficacy evaluations, two Baselines will be used, namely, the OLE study Baseline and the original (i.e., parent) study Baseline, as applicable.

All data used in analyses and/or collected during the study will be provided in listings.

A more detailed description of the planned summaries and analyses of the data collected in this OLE study will be provided in the Statistical Analysis Plan (SAP).

12.4.1 Study Completion, Premature Withdrawal, and Missing Data

Subject completion status and subject withdrawals, as described in Section 11.1 and 11.2 will be summarized.

In general, missing data will not be replaced or imputed for the main analyses of the exploratory efficacy endpoints and safety endpoints. Imputation may be performed for some endpoints as part of supportive or sensitivity analyses. Details of such imputations will be described in the SAP.

12.5 Safety Analyses

Ongoing AEs/AESIs/SAEs that first occurred during a parent study will continue to be reported in the parent study eCRF until resolution. An AE/AESI/SAE that **worsens**

during the OLE will be reported using the OLE study process. Only new treatment-emergent adverse events (TEAEs) including AEs, AESIs and SAEs that first occurred during the OLE study are to be reported using the OLE study process).

Interim analyses of safety will be performed and reported on a limited basis to satisfy requirements of study oversight, for example to IRB/IEC and Competent Authorities. These analyses may include the worsening of any TEAEs relative to the original parent study and relative to the OLE Baseline. The effect of cumulative dose and levoketoconazole treatment exposure may be evaluated as risk factors for increased AE incidence and severity. These limited analyses (e.g. common adverse reactions summary) will not be accompanied by assessments of potential benefits. Any unplanned interim efficacy analyses will be accompanied by unplanned interim safety analyses.

12.5.1 Extent of Exposure

Study drug exposure will be summarized as the average daily dose, cumulative dose, and total number of days on study drug. Total number of days on study drug will be calculated for each subject as the treatment stop date minus treatment start date plus one day.

The occurrence and timing of dose discontinuations as well as dose increases will be displayed in a listing. Reasons for discontinuation and dose increases will also be reported in the listing.

12.5.2 Adverse Events

AEs will be coded using MedDRA and graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03 [NCI CTCAE, 2010].

TEAEs will be of primary interest. The number and proportion of subjects reporting the following will be calculated and reported: any TEAE, drug-related TEAEs, serious TEAEs, TEAEs of special interest, severe TEAE, TEAEs leading to discontinuation of study drug, and TEAEs leading to withdrawal from the study will be computed. The most common TEAEs (frequency above 5%) will also be reported.

TEAE summaries will include frequency by levoketoconazole dose and all doses and relative onset time of TEAEs (e.g., by visit, by study days). Additional summaries and listings will be created to explore TEAE signals over time.

12.5.3 Clinical Laboratory Evaluations

A laboratory value (from LFTs, blood chemistry, hematology, urinalysis) that is within the central laboratory's normal range will be considered normal. A laboratory value that is outside the central laboratory's normal range will be considered an abnormal value. The number and percentage of subjects with abnormal laboratory values will be summarized for each scheduled visit. Shift tables by visit will be constructed. Differences in continuous laboratory values between Baseline and each scheduled assessment will be calculated for each analyte and summarized descriptively.

12.5.4 Vital Signs

HR, SBP and DBP will be measured in triplicate at each visit. The mean of these measurements will be used as the final value for each visit. Changes and shifts from normality from Baseline for each measurement at each visit will be summarized. In addition, values of clinical importance (Table 3) will be identified in the data listings.

Table 3 Vital Sign Values of Clinical Importance

Vital Sign	Criteria	Flag
Heart Rate (HR)	below 44 bpm	Low (L)
	44-100 bpm	Normal
	101-120 bpm	High (H)
	above 120 bpm	Very High (VH)
Systolic Blood Pressure (SBP)	below 90 mm Hg	Low (L)
	90-139 mm Hg	Normal
	140-169 mm Hg	High (H)
	170 mm Hg and above	Very High (VH)
Diastolic Blood Pressure (DBP)	below 50 mm Hg	Low (L)
	50-89 mm Hg	Normal
	90-109 mm Hg	High (H)
	110 mm Hg and above	Very High (VH)

12.5.5 Electrocardiograms (ECGs) and QTc Intervals

Summary ECGs, based on the measurement of ECGs as described in Section 6.2.3 will be used for each evaluation. Quantitative ECG measurements (PR interval, QRS duration, HR, QT interval, QTcB interval, and QTcF interval) and changes from Baseline will be summarized descriptively by dose and time point. ECG results will be available to the Investigator shortly after being obtained and all ECGs will be reviewed by a central reading by Spaulding who will provide an "over-reading" that will serve as the definitive study value. While on study treatment, a QTcF above 500 msec or above 60 msec above OLE Baseline will be an AESI (See Section 14.1).

Categorical changes from Baseline (increases only) and QTc values from each visit will be summarized by worst change and by visit and by dose of levoketoconazole. The clinically important categories (Table 4) of actual and change values will be tabulated and provided as listings.

Table 4. QTc Interval Values of Potential Clinical Importance

QTc Interval	Criteria (msec)
Increase from Baseline	<30
	30-60
	above 60
Actual Value	451-480
	481-500
	above 500

12.5.6 Other Safety Measures

All other safety laboratory measures (e.g. morning serum cortisol, ACTH) will be listed by subject and time point and descriptively summarized, including changes from Baseline by dose of levoketoconazole.

Changes in the size of pituitary tumor (in millimeters largest diameter and/or estimated volume), if estimable, from Baseline will be summarized descriptively.

Clinically significant physical examination findings after the first dose of levoketoconazole in the OLE study will be reported as AEs by the Investigators. All physical examination findings will be listed.

12.6 Efficacy Analyses

The overall strategy for the efficacy analyses will be to evaluate the changes or shifts in the efficacy endpoints relative to the OLE and original parent study Baselines, as applicable. All efficacy endpoints are considered exploratory. Results will also be compared between the two parent studies, as applicable. The primary analysis approach will be to calculate point estimates and construct two-sided 95% confidence intervals. P-values from statistical tests for significance will be calculated for descriptive purposes only. For continuous endpoints, the change from each of the two Baselines to each regular visit in the OLE study, including the final visit, will be calculated. The 95% confidence interval for the mean change and corresponding p-value will be calculated using paired t-test. For categorical endpoints, the shifts from each of the two Baselines to each regular visit in the OLE study, including the final visit, will be presented. The 95% confidence interval for the difference in the paired proportions will be calculated using the adjusted Wald method, and the shifts will be evaluated for significance using McNemar's test or Bowker test of symmetry. The mean changes from Baseline to each regular visit will be compared between the parent studies using unpaired t-test for continuous endpoints, and the proportions at each regular visit will be compared between the parent studies using Fisher's Exact test for categorical endpoints.

12.6.1 UFC and LNSC Analyses

The number and proportion of subjects with mean UFC (mUFC) and LNSC less or equal to the ULN will be summarized at each visit. In addition, the numbers and proportions of subjects with mUFC above the ULN to 1.5X the ULN and above will be summarized at each visit. Shifts from Baseline will be evaluated using McNemar's test or Bowker test of symmetry.

Changes in UFC and LNSC from Baseline

The mUFC will be calculated from adequate 24-hour urine collections only. The mUFC will be calculated only if there are at least two adequate samples. The mUFC from the collections at each visit will be used in the analysis of UFC unless only one adequate sample is available, in which case the single sample will substitute for the mUFC.

The mUFC will be summarized by time point using descriptive statistics and displayed over time. Paired t-tests will be performed for the change from Baseline to each nominal visit.

12.6.2 Clinical Signs and Symptoms

Individual clinical signs and symptoms, defined in Appendix L, will be summarized at each time point for assessment by number and percent of subjects. For signs and symptoms other than acne, hirsutism and edema, each sign and symptom present at Baseline will be graded on a 0 to 3 severity scale (0=none, 1=mild, 2=moderate, 3=severe), and the severities reported at each visit will be added to derive a total score. Total severity score and changes from Baseline of the severity total score will be presented by visit. Acne, hirsutism, and edema scores will be calculated as per their respective instrument-derived instructions, and results will be summarized at each visit, including changes from Baseline.

A paired t-test will be used to test if there is a significant change in severity at each visit. In addition, shift tables in individual clinical signs and symptoms at each visit will be created to demonstrate any changes during the course of treatment and will be analyzed using McNemar's test or Bowker test of symmetry.

12.6.3 Cushing's Syndrome Quality of Life Questionnaire

QoL (Appendix K) measures and changes from Baseline will be summarized by time point using descriptive statistics and analyzed using a paired t-test.

12.6.4 Beck's Depression Questionnaire

Changes from Baseline for the Beck's Depression questionnaire (Appendix M) will be summarized by time point using descriptive statistics and analyzed using a paired t-test.

12.6.5 CS Comorbidity Biomarkers

The changes from Baseline and percentage changes from Baseline in individual biochemical markers of CS comorbidities (FBG, fasting insulin and HOMA-IR, HbA1c, blood pressure, total cholesterol, HDL-C, LDL-C, and high-sensitivity CRP) will be summarized by time point using descriptive statistics and the changes from Baseline will be analyzed using a paired t-test. In addition, shifts from Baseline (with regards to laboratory normal range) in individual biochemical markers of CS comorbidities will be analyzed using Bowker test of symmetry at each scheduled visit.

12.6.6 Usage of Anti-diabetic, Anti-cholesterol, and Anti-hypertensive Therapies

The number and proportion of usage of each medication class of interest at Baseline and at all post-Baseline visits by treatment will be displayed. In addition, the number and proportion of subjects with medication changes during the study will be summarized by time point. The proportions with dose increases and decreases, including new and discontinued medications will be displayed.

12.6.7 Compliance (Adherence) and Persistence with Therapy

Study drug compliance between visits and cumulative study drug compliance will be calculated by dividing the number of study drug tablets used (total number dispensed

minus total number returned/lost/wasted) by the total number of study drug tablets that should have been taken and multiplying the result by 100. Study drug compliance will be summarized. Persistence with therapy will be assessed by the number and proportion of subjects who complete 1, 2, and 3 years of treatment in this OLE study, with at least 80% compliance with study drug.

12.7 Subgroup Analyses

Subgroup analyses for selected exploratory efficacy endpoints and safety endpoints will be performed for a minimum subgroup size of at least 15 subjects. The subgroups of interest will include, but not be limited to, subgroups based on diagnosis of CD, prior therapy for CS, hypertension at Baseline, and prediabetes or diabetes at Baseline. Details will be presented in the SAP.

13 ADVERSE EVENTS (AE) AND SERIOUS ADVERSE EVENTS (SAE)

The Investigator and study staff are responsible for detecting and recording AEs and SAEs during scheduled safety evaluations and whenever such information is brought to their attention. This section of the protocol provides definitions and detailed procedures to be followed.

During each visit, the Investigator will question the subject about AEs using an open question taking care not to influence the subject's answers, e.g. "have you noticed any change in your health?"

13.1 Definition of an AE

An AE is any untoward medical occurrence in a study subject that is temporally associated with the use of a medicinal product, regardless of its potential relationship to the medicinal product. An AE, therefore, can be any unfavorable or unintended sign, including an abnormal laboratory finding, symptom, or disease (new or exacerbated), whether related to the study drug or study conduct or not.

Examples of an AE include:

- Exacerbation of a pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study.
- Signs, symptoms of a drug interaction.
- Signs, symptoms of a suspected overdose of either investigational product or a concurrent medication.
- A laboratory abnormality worsening or newly occurring after the start of the study (i.e., after the OLE Baseline Visit) that results in subject withdrawal from the study or medical treatment or further follow-up.

NOTE: Abnormal values that reflect hypercortisolism (UFCs, LNSC and serum cortisol) will not be recorded as AEs. AEs may include pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of subject's previous therapeutic regimen).

13.2 Definition of a SAE

An SAE is any untoward medical occurrence that, at any dose:

(a) results in death;

(b) is life-threatening;

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if it were more severe.

(c) requires hospitalization or prolongation of existing hospitalization;

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out - patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, or was necessary, the AE should be considered serious.

(d) results in disability/incapacity;

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

(e) is a congenital anomaly/birth defect, or

(f) Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

13.2.1 Disease-Related Events

Although symptoms of CS are quite non-specific, all AEs and their attributions will be collected and reviewed. The reduction in cortisol levels, regardless of therapeutic intervention, is known to cause symptoms (e.g., nausea, lethargy, muscle aches), and these too will be captured as AEs for evaluation.

13.2.2 Adverse Events of Special Interest (AESI)

Adverse Events of Special Interest are defined in Section 14.

AESIs should be reported to the Sponsor's designated safety group with 24 hours as per Section 13.7 regardless of seriousness or causality. Upon receipt, these AEs will be captured in the safety database and targeted follow-up queries will be sent to sites.

13.3 Timing, Frequency, and Method of Detecting AEs and SAEs

As a consistent method of soliciting AEs, the subject should be asked a non-leading question such as: "How do you feel?"

Ongoing AEs/AESIs/SAEs that first occurred during a parent study will continue to be reported in the parent study eCRF until resolution. An AE/AESI/SAE that **worsens** during the OLE will be reported using the OLE study process. In addition, any new AEs, AESIs and SAEs that first occurred during the OLE study (after subject completes parent study) are to be reported using the OLE study process. All new AEs must be recorded irrespective of whether they are considered drug-related.

At each visit/assessment in the period defined above, AEs will be evaluated by the Investigator and recorded.

Any AEs already documented at a previous assessment and designated as ongoing, should be reviewed at subsequent visits as necessary. Resolution of AEs should be documented to include the date of resolution and any interventions made. Changes in intensity or frequency of AEs should be recorded as separate AEs (i.e., a new event record started).

13.4 Recording of AEs and SAEs

All clinical events, including either observed or volunteered problems, complaints or symptoms are to be recorded on the AEs page(s) of the eCRF. The need to capture this information is not dependent upon whether the clinical event is associated with study treatment. Adverse clinical events resulting from concurrent illnesses or reactions to concurrent medications are also to be recorded. To avoid vague, ambiguous, or colloquial expressions, the AE should be recorded in standard medical terminology rather than the subject's own words.

Each adverse clinical event is to be evaluated for duration, intensity, and whether the event may be associated with the study drug or other causes. Start and stop dates, relationship to study drug, medical management, and presumed cause of the event (if not thought to be study drug related) must be recorded in the AEs section of the eCRF. AEs believed to be possibly related to study drug must be followed until event resolution or a minimum of 30 days after the last dose of levoketoconazole.

13.5 Evaluating AEs and SAEs

13.5.1 Severity Rating

The severity of AEs and SAEs will be graded per NCI CTCAE, Version 4.03.

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

An AE that is assessed as severe should not be confused with an SAE. An event is defined as 'serious' when it meets one of the predefined outcomes as described in Section 13.2 "Definition of a SAE".

13.5.2 Relationship to Study Drug

The relationship to study treatment is to be assessed using the following definitions:

- **Not related:** The AE is definitely not related to the drug. This designation should be reserved for those events which occur prior to study treatment or for those events which cannot be even remotely related to study participation (e.g., injuries sustained in an automobile accident that itself was not precipitated by a possibly related AE).
- **Unlikely:** There is no reasonable association between the study treatment and the suspected event, and a precipitant of the AE other than study treatment has been identified (e.g., a therapy used outside of the study or the subject's underlying clinical condition).
    - For purposes of expedited regulatory reporting, unlikely causality will be considered as not related causality.
- **Possibly related:** The suspected event may or may not follow a reasonable temporal sequence from study treatment administration but seems to be the type of reaction that cannot be dismissed as unlikely. The event could have been produced or mimicked by the subject's clinical state or by other modes of therapy concomitantly administered to the subject.
- **Probably related:** The suspected event follows a reasonable temporal sequence from study treatment administration, abates upon discontinuation of the treatment, and cannot be reasonably explained by the known characteristics of the subject's clinical state.

- **Definitely related**: This designation should be reserved for those events which have no uncertainty in their relationship to treatment administration.

13.6 Follow-Up of AESIs and SAEs

After the initial AESI/SAE report, the Investigator is required to follow the event status actively. Further information on SAEs should be provided to the Sponsor's designated safety group on the subject's condition within 24 hours as described in Section 13.7.

New or updated information on SAEs should also be recorded on the "SAE" eCRF within 24 hours.

13.7 Prompt Reporting of SAEs and AESIs to Sponsor

Any SAE reported by a subject who has signed the informed consent whether during the study or discovered during follow-up, must be reported by the Investigator to the Sponsor's designated safety group **within 24 hours** even if the SAE does not appear to be drug-related. This should be done by emailing or faxing a copy of the SAE Report form plus other related information to Sponsor's designated safety group. The SAE may be reported by telephone; however, this should be followed up within 24 hours with a copy of the SAE Report form. Additionally, it may be necessary for the designated safety group to communicate with the Investigator if additional information is required.

Regardless of seriousness or causality, AEs designated as AESIs (instances of persistent QTc prolongation, potential hepatic events, and potential adrenal insufficiency) should be reported to the Sponsor's designated safety group within 24 hours, in the same manner as SAEs (see also Section 13.7).

During both business and non-business hours, the email address listed below should be used to report SAEs and AESIs.

Reportable Events Hotline

Email: GlobalSAEInbox@Chiltern.com

An SAE Report form must be completed and forwarded via email to the Sponsor's designated safety group using the email address listed above within 24 hours of becoming aware of the event.

All additional follow-up evaluations must be reported to the Sponsor's designated safety group. Such data should be sent to the Sponsor within 24 hours. All SAEs will be followed until the Investigator and Sponsor agree the event is satisfactorily resolved.

The Sponsor will be responsible for completing the safety report and for notifying the relevant authorities of any SAE as outlined in the International Conference on Harmonization (ICH) Guidelines and per local regulatory requirements. The Investigator and the Sponsor's designated safety group will also ensure that the appropriate IRBs/ IECs are notified of the SAE.

14 ADVERSE EVENTS OF SPECIAL INTEREST (AESI): DEFINITIONS AND MANAGEMENT

An AESI is defined as a serious or non-serious event of scientific and medical concern specific to a Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor can be appropriate.

The AESIs for this study are defined in the sections that follow along with instructions for the management of AESIs.

14.1 Persistent QTc Prolongation:

Persistent elevation of the QTc interval is defined as absolute QTc interval above 500 msec (or above 60 msec above the OLE Baseline), with an ECG evaluation on repeat determination continuing to demonstrate QTc prolongation in the absence of plausible alternative explanations.

Determination of persistent and confirmed QTc prolongation

To decide whether a QTc prolongation is persistent and likely to be related to levoketoconazole, QTc will be evaluated via central reading of the ECG by Spaulding. The Investigator should consider alternative possibilities as causative or contributory to QTc prolongation prior to discontinuation of levoketoconazole, including concomitant medications that may result in prolongation of the QTc interval either directly or through interference with the metabolism of levoketoconazole, recent food ingestion (temporary QTc elevation), and electrolyte abnormalities (particularly serum calcium, magnesium and potassium). Interfering concomitant medications with QT prolongation potential are contraindicated in co-administration with levoketoconazole and must be stopped (Section 10.2). Please see Appendix N for guidance on the assessment of apparent QTc interval prolongation. Regardless of seriousness or causality, instances of persistent QTc prolongation should be reported to the Sponsor's designated safety group within 24 hours from the time the persistent prolongation has been confirmed, in the same manner as SAEs (see Section 13.7).

In the event QTc prolongation occurs additional safety monitoring is required, including medical observation of the subject until the QTc interval has returned to a value less than or equal to 500 msec.

Additional evaluation of the subject will include the potential requirement for additional ECGs and laboratory assessments (see Appendix N). Cases of persistent, confirmed QTc prolongation as described above should be reported to Sponsor's designated safety group as AESIs (Section 13.7).

14.1.1 Temporarily Stopping Study Medication for Prolonged QTc and Considerations for Restarting

If the subject is receiving doses greater than 150 mg/day, persistent and presumed study medication-related QTc changes may be managed by temporarily withholding study medication if deemed necessary. Note that a prolonged QTc interval that is less than 500

msec may not always warrant temporary medication stoppage, depending on patient-specific clinical factors, e.g. if the QTc does not exceed normal reference values (ULN for men is 440 msec and for women is 460 msec).

Withheld study medication may be resumed at the same or lower dose after resolution of QTc prolongation is confirmed by two ECG readings and with prior approval by the Medical Monitor. After restart of study medication, ECG evaluation should occur within 1 to 2 hours of dosing, and future ECG monitoring should be continued per the visit schedule to monitor.

Temporarily withheld study medication for QTc prolongation may be resumed using the prior regimen, after confirmed QTc correction. However, unless an etiology other than study drug has been implicated, QTc prolongation reoccurrence above 500 msec will usually result in permanent study medication discontinuation and study withdrawal unless the dose can be lowered permanently (see Section 14.1.2).

14.1.2 Withdrawal due to QTc Interval Prolongation

If a persistent and confirmed levoketoconazole-related QTc interval prolongation above 500 msec as defined in Section 6.2.3 is identified, the Investigator should attempt to manage such QTc prolongations by temporarily stopping study medication followed by dose reduction if doing so does not eliminate the benefits of treatment. If therapeutic benefit cannot be maintained following dose reduction for drug-induced QTc prolongation above 500 msec, study medication should be stopped permanently and the subject should be withdrawn.

If a persistent and confirmed levoketoconazole-related QTc interval prolongation above 500 msec is observed at the lowest levoketoconazole dose (150 mg/day), administration of levoketoconazole should stop permanently and the subject should be withdrawn.

Persistent, confirmed levoketoconazole-related QTc interval prolongation that represents an increase greater than 60 msec from baseline but that may not be of sufficient duration to cause concern of arrhythmias (e.g. less than 440 msec in men or less than 460 msec in women), depending on other clinical factors (e.g. recalcitrant hypokalemia) need not be managed with dosage reduction or result in withdrawal.

Additional information for QTc Interval is available in Appendix N.

14.2 Hepatic Abnormalities:

Signs and/or symptoms indicative of hepatic dysfunction or injury, including asymptomatic but clinically relevant abnormalities of LFTs, should be reported as an AE, AESI, or SAE, as applicable. Events meeting the below criteria should always be reported as either an AESI or SAE, as applicable, and should prompt temporary (or permanent—see below) study medication interruption:

- ALT or AST above 8X ULN;
- ALT or AST rises to above 5X ULN in less than 4 weeks or persists for over 2 weeks;
- ALT or AST above 3X ULN and TBN above 2X ULN not explained by any other cause such as viral hepatitis;

- ALT or AST above 3X ULN with new onset of or worsening of fatigue, nausea, vomiting, fever, rash or eosinophilia, in the absence of other evident cause, or
- Signs and /or symptoms suggestive of hepatic dysfunction (any of the following: nausea, anorexia, fever, fatigue, right upper quadrant discomfort, pruritus, dark urine or acholic stool) coupled with ALT and/or AST above 3X ULN and/or AP above 2X ULN, and/or TBN above 2X ULN in the absence of evidence for obstruction or Gilbert syndrome. An ultrasound evaluation of the gallbladder and bile duct should be conducted to exclude cholestasis as the cause for elevated AP and/or TBN.

Please see Appendix N for guidance on the assessment of abnormal LFTs and Section 14.2.1 for monitoring abnormal LFTs

14.2.1 Safety Monitoring and Dose Interruptions for Hepatic Abnormalities*:*

When a clinically significant liver test abnormality is observed, the battery of liver Screening tests should be repeated as soon as possible after initial determination of the abnormality and thereafter at 3- to 4-day intervals or as the clinical situation dictates.

If ALT and/or AST levels at any time exceed 8X ULN or if AST/ALT are persistently higher than 5X ULN and are accompanied by a concurrent rise on TBN, or if abnormal liver safety test studies are accompanied by clinical signs or symptoms referable to liver injury, the study medication **must be interrupted** immediately.

The need for levoketoconazole interruption will be influenced by the Baseline liver safety test values and the subject's clinical condition at the time of the abnormal liver safety test finding. For example, small increases in ALT/AST above a subject's Baseline concentration that are unaccompanied by symptoms may not warrant any medication interruption, whereas large increases from a subject's Baseline, even if not too high absolute concentrations, might warrant withholding medication temporarily. Even if ALT and/or AST continue to rise slowly (**but only if** unaccompanied by a concurrent rise in TBN exceeding the cut-offs for study drug cessation/early withdrawal), asymptomatic subjects may continue to receive study medication uninterrupted with cautious monitoring, depending on the clinical condition.

If on serial measurements and in the absence of clinical signs or symptoms, the ALT and/or AST continue to rise and do not meet the criteria for immediate treatment interruption, subjects may continue levoketoconazole without interruption.

If abnormally elevated liver safety tests return to the subject's OLE Baseline while the subject continues to be dosed with study medication, serial, frequent liver safety test measurements may be discontinued, with usual safety monitoring thereafter.

Appropriate diagnostic evaluations and interventions should be implemented based on the clinical presentation of the subject and following the instructions for AESI-liver safety test abnormality follow-up (Appendix N).

Rechallenge with Study Medication

If levoketoconazole dosing has been interrupted and liver safety tests normalize, subjects may be rechallenged (i.e. restarted on medication at prior or lower dose) at the discretion

of the Investigator AND following discussion with and approval by the Medical Monitor. Note that rechallenge has been associated with relatively more severe liver injury among some patients treated with ketoconazole who interrupted medication temporarily [Ketoconazole 2014 HRA Assessment Report]. Therefore, it is important to recheck liver safety tests within 4 days after rechallenge or earlier if the subject develops symptoms referable to acute liver injury and recheck them again 7 to 10 days later. Subjects who are uneventfully rechallenged may remain in the study with usual safety monitoring thereafter.

14.2.2 Withdrawal due to Abnormal Liver Function Tests

Any event qualifying as an AESI or SAE as per Section 14.2 may prompt consideration of study withdrawal. However, Section 14.2.1 describes monitoring and management procedures that may be followed in lieu of withdrawing from medication permanently, as the clinical condition warrants.

If ALT and/or AST levels at any time exceed 8X ULN or if AST/ALT are persistently higher than 5X ULN and are accompanied by a concurrent rise on TBN, or if abnormal liver safety test studies are accompanied by clinical signs or symptoms referable to liver injury, the study medication must be stopped immediately. In nearly all such cases, study medication should not be restarted owing to the heightened risk of liver injury, and the subject will discontinue from the study and be followed until resolution or normalization of the laboratory abnormality that resulted in the withdrawal.

If other clinically significant LFT elevations persist beyond 4 weeks after interruption of therapy or demonstrate a trend of worsening following interruption, then the subject should be withdrawn from the study. The subject should continue to be followed after withdrawal until resolution or normalization of the laboratory abnormality that resulted in the withdrawal.

More detailed information on evaluation of LFTs is available in Appendix N.

14.3 Adrenal Insufficiency

It is well recognized that subjects with a good response to treatment for CS resulting in decreased, but not low, cortisol concentrations may exhibit signs and symptoms of adrenal insufficiency (not life-threatening) which may not be different than those of acute adrenal crisis, which is a life-threatening event warranting immediate medical intervention. Discrimination between the two may not be readily evident by history or physical examination. Furthermore, subjects may have adrenal insufficiency without abnormal cortisol concentrations, but the cortisol concentrations, while within or above the normal range, are inappropriately low for the degree of physiological stress being experienced.

Symptoms attributable to adrenal insufficiency may include: nausea, vomiting, abdominal pain, anorexia, malaise, fatigue, headache, arthralgias/myalgias, gastrointestinal discomfort, dizziness (particularly upon standing), irritability, depression, sweating, and fever. Signs of adrenal insufficiency are few and uncommonly observed, but postural hypotension and hypoglycemia can occur.

All medical care providers identified by the subject, in addition to the Investigator, MUST be given sufficient written instructions about the potential risks of adrenal insufficiency associated with the use of cortisol synthesis inhibitors, such as levoketoconazole.

14.3.1 Safety Monitoring for Adrenal Insufficiency

Subjects with suspected adrenal insufficiency should be assessed for signs and symptoms of adrenal insufficiency and cortisol levels as described above.

Should adrenal insufficiency be deemed present or probable, study drug should be temporarily discontinued for mild symptoms/signs. For moderate or severe symptoms/signs, study drug should be temporarily discontinued and rescue glucocorticoids administered as indicated. Study drug at the same or an appropriately lower dose may be restarted once the medical situation is deemed sufficiently resolved by the Investigator. Cases of suspected adrenal insufficiency should be reported to Sponsor's designated safety group as AESIs (Section 13.7).

If the dose associated with adrenal insufficiency is the lowest dose of 150 mg/day, the subject might be exhibiting exquisite sensitivity to the cortisol-lowering effects of levoketoconazole. In such cases, the subject should be informed of the heightened risk of future occurrences of adrenal insufficiency before resuming study medication with consideration given to permanent drug discontinuation.

Subjects should be assessed for symptoms and objective measures relatable to adrenal insufficiency as follows:

- Random serum cortisol as close to the onset of the event as possible and (if possible) morning serum cortisol. Laboratory evidence of hypoadrenalism is defined as morning serum cortisol level less than 3 µg/dL ([LLN] or the lower limit of the assay being used for clinical testing). Even if serum cortisol and/or 24-hour UFC are within the normal range, the possibility of adrenal insufficiency should be considered, based on other clinical signs and symptoms. Please see Appendix J for a list of clinical signs and symptoms;
- Full review of systems;
- Lying and standing blood pressure measurements and pulse to evaluate postural changes;
- Random glucose and electrolytes;

All cases of suspected adrenal insufficiency, whether deemed to be drug-related or not, should be reported as AESIs to the Sponsor/CRO (Section 13.7).

15 REFERENCES

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APPENDIX A TIME AND EVENTS SCHEDULE

Refer to the Section 6 (Study Assessments and Procedures) and the Study Procedures Manual for more specific details on the assessments.

Assessments	Screening	Baseline	Every 3 Months (± 7 Days)	Every 6 Months (or 12 Months if indicated) (± 10 Days)[11, 13]	Dose Adjustment / Safety Monitoring Visit[12,14]	Final Study Visit	Safety Follow-Up Call[15]
COR-2012-01 Visit Alignment[1,2]	M9	M12					
COR-2017-01 Visit Alignment[1,2]	RES1	RES2					
Expanded Access Program	Screening & Baseline should occur within 3-4 weeks of each other						
Informed Consent	X						
Eligibility Check	X	X					
Prior/concomitant Medications	X[3]	X[3]	X		X	X	
Pregnancy Test (urine βhCG), females	X[3]	X[3]	X		X	X	
Adverse Events	X[3]	X[3]	X		X	X	X
ECG (central read) [4]	X[3]	X[3]	X		X	X	
Vital Signs (temperature, BP, heart rate) [5]		X[3]	X		X	X	
Body weight/height/BMI (derived)		X[3]	X		X	X	
Physical Examination		X[3]		X		X	
CS Signs and Symptoms		X[3]		X		X	
Safety Laboratory Tests (including hematology, chemistry, LFTs, urine dipstick)[6]	X[3]	X[3]	X		X	X	
Serum Cortisol (am)		X[3]	X		X	X	
Late Night Salivary Cortisol (2 nights)		X[3, 7]	X		X	X	
ACTH		X[3]		X	X	X	
24-h UFC (2-3 collections)[8]		X[3]		X	X	X	
CS Biomarkers FBG, fasting insulin, HOMA-IR, HbA1C, total cholesterol, HDL-C, LDL-C, hsCRP		X[9]		X		X	
Pituitary MRI (pituitary tumor patients only)		(X) [10]		X[10, 13]		X	

Assessments	Screening	Baseline	Every 3 Months (± 7 Days)	Every 6 Months (or 12 Months if indicated) (± 10 Days)[11, 13]	Dose Adjustment / Safety Monitoring Visit[12,14]	Final Study Visit	Safety Follow-Up Call[15]
Cushing QoL questionnaire		X[3]		X		X	
BDI-II instrument		X[3]		X		X	
Subject Diary	X[16]	X	X		X		
Dispense drug		X	X				
Administer drug and/or drug accountability		X	X		X	X	

1 Procedures performed during the listed parent study visits should not be repeated for the OLE. Rather the OLE will make use of data already captured for these parent study visits. The informed consent and eligibility check may occur on a date that is different from the parent study clinic visit, if this is completed > 1 month prior to the anticipated date for the end of treatment on the parent study.

2 This Time and Events Schedule does not account for additional tests that need to be collected as part of COR-2012-01 or COR-2017-01, for subjects whose parent study visits align with OLE Screening and/or Baseline. Refer to parent study's respective Time and Events Schedule.

3 Assessment overlaps with parent study.

4 12-lead ECGs should be obtained prior to first dose of drug as a Baseline and every 3 months (or after dose increases) after enrollment. ECGs should be obtained within approximately 1 to 2 hours after drug administration and after the subject has rested in a supine position for at least 5 minutes after the subject has not eaten for at least 2 hours. NOTE: For subjects entering from Study COR-2012-01 the Spaulding device previously used in the parent study is not planned for use in this OLE study. However, it is acceptable to use the prior device for the OLE Screening and/or Baseline Visit.

5 BP and heart rate will be done in triplicate.

6 If urine dipstick is positive for protein and ketones, send urinalysis to the lab for assessment.

7 Ensure that **2** collections are done immediately prior to Baseline and results are available

8 Three collections of 24-hr UFC will occur at every visit marked in the Time and Events Schedule, except for if a subject's OLE Baseline Visit overlaps with M12 (as part of COR-2012-01), then 2 collections will be collected.

9 hsCRP and fasting insulin are not assessed in COR-2012-01 but are assessed in this OLE study, in addition to performing the parent study's assessments (including CRP) if M12 aligns with OLE Baseline, Investigators would also conduct a hsCRP and fasting insulin assessment at Baseline.

10 If not done within 6 months of the OLE Baseline Visit.

11 Assessments listed here are **in addition** to those done every 3 months.

12 Dose Adjustment/Safety Monitoring Visits will be conducted in accordance with the requirements specified in Section 6.1.6.

13 Annually (the scheduled interval between MRIs should be once every 12 (± 2) months).

14 Liver Function tests (AST, ALT, GGT, AP, LDH, total and direct bilirubin) to be done biweekly for 1 month (twice in total) unless total daily dose is greater than 600 mg, then weekly (4 times for 1 month), 12-lead ECG (to check for evidence of QTc prolongation) to be conducted 1 to 2 hours after dosing at the new (higher) dose and again after 1 month and cortisol monitoring (e.g. UFCs, Serum Cortisol, Salivary Cortisol) biweekly for 1 month (twice in total).
15 Safety Follow-Up Call to be conducted 1 week following the Final Study Visit
16 To be dispensed for subjects entering from Expanded Access Program or for those that had a gap in treatment with levoketoconazole

APPENDIX B LABORATORY ANALYTES

Laboratory studies to be collected as per Time and Events Schedule (Appendix A). Other analytes may be required to follow-up certain abnormalities. While the central laboratory will be used for most analytes, in some cases additional studies may be assayed at a local laboratory, for example, when a rapid result is needed; prior discussion with the Medical Monitor is suggested. For example, AESIs and SAEs indicative of liver injury will usually require additional laboratory tests that will need to be sent to the central laboratory in addition to the local laboratory.

Routine Clinical Laboratory Tests

Hematology

Platelet Count	***RBC Indices*:**	***Automated WBC Differential:***
RBC Count	MCV	Neutrophils
WBC Count (absolute)	MCH	Lymphocytes
	MCHC	Monocytes
Hemoglobin		Eosinophils
Hematocrit		Basophils

Clinical Chemistry

Blood Urea Nitrogen	Albumin
Creatinine	Total Protein
Glucose, fasting	
Sodium	***Liver Function Tests (LFTs)***
Potassium	AST (SGOT)
Chloride	ALT (SGPT)
Total CO_2	GGT
Calcium, Magnesium, Phosphate	Alkaline phosphatase
Uric Acid	Total and direct bilirubin
	LDH

Other analytes/measures

Urine dipstick: if positive for protein or ketones, send urinalysis to central laboratory for assessment

Pregnancy test (urine βHCG, women only)

Disease-related Assessments

Urinary free cortisol, total creatinine and total volume from 24-hour urine collections

Salivary cortisol

Serum cortisol

ACTH

CS Biomarkers

Fasting blood glucose [FBG]

Fasting Insulin

Hemoglobin A1c [HbA1c]

High-sensitivity C-reactive protein [hsCRP]

Total cholesterol

High-density lipoprotein-cholesterol [HDL-C]

Low-density lipoprotein-cholesterol [LDL-C]

APPENDIX C STUDY MANAGEMENT AND MATERIALS

Study Documentation

The Investigator is required to prepare and maintain adequate and accurate case histories (i.e., source documents and/or Medical Record Supplement) designed to record all observations and other data pertinent to the study for each study participant. This includes accurate documentation of accountability of study medications. The medical records must contain adequate information to allow for verification of subject identity throughout the study.

Electronic CRFs (eCRFs) will be completed for each subject who is enrolled in the study. Subject numbers will be assigned systematically immediately following the execution of written informed consent. A subject Screening/enrollment log, noting reasons for screen failure where applicable, will be maintained for all subjects who are consented.

All information recorded on the eCRFs for this study must be consistent with the subject's source documentation (i.e., source documents and/or Medical Record Supplement). The source documents may include the hospital and/or the physician's chart, X-rays, or laboratory test documentation.

The eCRFs for each subject will be periodically checked against the subject's source documents at the study site by the site monitor. Instances of missing or unclear data will be discussed with appropriate site personnel for resolution. A quality assurance audit will be performed on the database.

Archiving of Study Documentation

The Investigator shall retain records for two years following the date that a marketing application is approved for the indication pertaining to this clinical study; or, if the drug is planned to be terminated or if a regulatory application is not planned to be progressed, until two years after the investigation is discontinued and the Food and Drug Administration (FDA) or a competent regulatory authority is notified.

The Sponsor will inform the Investigator, in writing, as to when these documents no longer need to be maintained.

Monitoring and Quality Assurance

During the study, a monitor will make routine site visits to review protocol compliance, compare eCRFs with individual subject's original source documents, assess drug accountability and ensure that the study is being conducted per pertinent regulatory requirements. The review of the subjects' original medical records will be performed in a manner to ensure that subject confidentiality is maintained.

APPENDIX D ADMINSTRATION AND REGULATORY POLICIES

Ethical Conduct of Study

The Investigator(s) should conduct the study in accordance with this protocol, the Declaration of Helsinki, ICH GCP guidelines and FDA regulations. The Investigator(s) and the Sponsor will sign the protocol and study contract, to confirm agreement. The Investigator(s) will not implement any amendment (deviation or changes of the protocol) without agreement by the Sponsor and IRB/IEC approval, except where necessary to eliminate immediate hazard(s) to study subjects, or when change(s) involve only logistical or administrative aspects of the study.

Records that may reveal the identities of subjects must be well protected, with consideration given to confidentiality and the right to privacy of subjects.

Informed Consent

Each subject or his/her parent/legal representative must be provided with a statement that the investigation involves research and that the IRB/IEC has approved solicitation of subjects to participate; a fair explanation of the procedures to be followed and their purposes, including identification of any procedures that are experimental; a description in lay language of any possible side effects; a description of any attendant discomforts and risks reasonably to be expected; a description of any benefits reasonably to be expected; a disclosure of any appropriate alternative procedures that might be advantageous for the subject; an offer to answer any inquiries concerning the procedures, and instruction that the person is free to withdraw consent and discontinue participation in the project or activity at any time without prejudice to the subject. Payment to research subjects for participation in the study is considered a benefit. All information concerning payment, including the schedule of payments, must be set forth in the informed consent, including a disclosure that the Investigator is being paid to perform the stated research.

A subject (or the subject's legally authorized representative) must give written consent to participate in the study. This consent must be dated and retained by the Principal Investigator as part of the study records. A copy shall be given to the person signing the form. The informed consent process must be documented in the subject's source documents.

The Investigator agrees that the Sponsor, its employees or agents will have the right from time to time during this study to audit and review pertinent medical records relating to this clinical trial. A statement will be obtained from each subject participating in the study permitting the release of his/her medical records as necessary for inspection by authorized personnel of the Sponsor, FDA, other Competent Authorities and the staff managing the clinical study.

The release of medical records and review of their contents will comply with the Health Insurance Portability and Accountability Act of 1996 and applicable data protection regulations in the countries concerned.

Institutional Review/Ethical Review

The protocol and ICF for this study must be approved by an IRB/IEC. A copy of the Letter of Approval from the Board/Committee, which contains specific identification of

the documents approved, must be received by the Sponsor prior to shipment of drug supplies to the Principal Investigator.

All changes to the protocol, as well as a change of Principal Investigator, must also be approved by the Board/Committee and documentation of this approval provided to the study monitor. Records of the IRB/IEC's review and approval of all documents pertaining to the study must be kept on file by the Principal Investigator and are subject to FDA/Competent Authority inspection at any time. IRB/IEC re-approval is required each year or per local regulations. The Principal Investigator is to notify the study monitor, in writing, of the approval to continue the study.

Clinical Monitoring/Record Keeping

There shall be no alterations in the protocol design without the written consent and approval of the Sponsor and the approval of the IRB/IEC, except in the case that subjects are at immediate risk without immediate implementation of such alterations. In such situations, the site should notify the Sponsor and IRB/IEC of the deviation as soon as possible, and should seek the written consent and approval of the Sponsor and the approval of the IRB/IEC.

All results of this trial must be recorded on eCRFs. Each subject who has been enrolled must have a completed eCRF. Reasons for termination must be stated in the early termination section. Study subjects are not to be identified by name on eCRFs, but rather by coded identifiers and/or subject initials.

The study monitor will verify the accuracy of the data by reviewing pertinent source documents such as office records or hospital charts of the subjects.

Study records include eCRFs, signed FDA Form 1572, original reports of test results, and signed ICFs. IRB/IEC approval letters and other documents pertaining to the conduct of the study are to be kept on file by the Investigator. If the study files are assigned to someone else or removed to another location, the Investigator is to notify the study monitor or Sponsor in writing of the change. All study records are subject to FDA or Competent Authority inspection at any time.

The Investigator shall retain records for a period as defined elsewhere (see Appendix C, Archiving of Study Documentation).

All information supplied to the Investigator by the Sponsor before, during, and after the study is confidential. Such information is to be used solely in connection with the clinical study. The study protocol, IB, and any other pertinent study-related materials or records provided are to be maintained in a confidential manner, reviewed carefully with attention to admonitions and returned to the Sponsor upon request. No part of these materials may be reproduced or transmitted in any form without prior written permission from the Sponsor.

APPENDIX E PUBLICATION POLICY

All data generated from this study are the property of Cortendo and shall be held in strict confidence along with all information furnished by Cortendo. Independent analyses and/or publication of these data by an Investigator or any member of his/her staff is not permitted without prior written consent of Cortendo.

Any formal presentation or publication of data from this trial will be considered as a joint publication by the Investigator(s) and appropriate Cortendo personnel. Authorships will be determined chiefly by merit—particularly impact on study design and conduct and experience with the study as determined by enrollment of subjects—with rights of final authorship decisions to be held by Cortendo, unless superseded by an agreement stipulating otherwise. The venue(s) selected for publication will be determined jointly by the publication authors. The first publication will be based on data from all study centers and analyzed as stipulated in the protocol and SAP. Investigators agree not to present data gathered from one study center or a subset of centers before the first full publication, unless formally agreed by Cortendo in advance. Written permission to Investigators to publish subset or secondary results will be contingent on prior review by Cortendo of the proposed methodology and analytical plan. Any Investigator-led publication or presentation will provide for nondisclosure of Cortendo confidential or proprietary information. In all cases, parties planning to publish data agree to submit all draft manuscripts or abstracts to Cortendo and other relevant parties at least 60 days prior to publication submission. This will enable involved parties to protect proprietary information and to provide comments to authors.

Further details on the publication process may be provided in individual contractual agreements signed by the Investigators and Cortendo.

APPENDIX F PROTOCOL AMENDMENT(S)

Each protocol amendment will be a stand-alone document. All revisions dictated by the amendments will be made in the protocol proper. A list of changes from the previous version will be provided. Each time a protocol is amended, a new amended version date will be added to the cover page.

APPENDIX G CRITERIA FOR DIAGNOSES OF PREDIABETES AND DIABETES

Reference: American Diabetes Association. Classification and diagnosis of diabetes. Sec. 2. In Standards of Medical Care in Diabetes—2016. Diabetes Care 2016;39(Suppl. 1):S13–S22.

The American Diabetes Association standards for the diagnosis of prediabetes consider three different categories of prediabetes, based on measures fasting glucose, HbA1c, or 2-hour postprandial glucose during a 75-gram oral glucose tolerance test (OGTT). For purposes of this study, however, the diagnosis of prediabetes will be limited to a single prediabetes category of impaired fasting glucose, as follows:

Prediabetes is defined by a fasting glucose of ≥ 100 mg/dL (5.6 mmol/L) and less than 126 mg/dL (7.0 mmol/L) (after no caloric intake for ≥ 8 hours and in the absence of antihyperglycemic medications).

Diabetes Is Diagnosed by One of the Following Criteria:

1. A fasting glucose of ≥ 126 mg/dL (7.0 mmol/L) after no caloric intake for ≥ 8 hours

OR

2. A random plasma glucose ≥ 200 mg/dL (11.1 mmol/L) associated with classic diabetes symptoms: increased urination, increased thirst and unexplained weight loss

OR

3. 2-hour post-glucose load plasma glucose ≥ 200 mg/dL (11.1 mmol/L) following oral ingestion of a 75-gram anhydrous glucose solution in water. NOTE: Oral glucose tolerance testing is not necessary if the subject has a fasting glucose level of ≥ 126 mg/dL.

OR

4. A1C ≥ 6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program-certified and standardized to the Diabetes Control and Complications Trial assay.

NOTE: In the absence of unequivocal hyperglycemia, results indicating diabetes should be confirmed by repeat testing using any of the above measures.

APPENDIX H GUIDELINES FOR HYPERTENSION

Reference: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), 2004

Table 5 Classification of Blood Pressure Levels for Adults Above 18 Years of Age

Blood Pressure Classification	SBP (mmHg)	DBP (mmHg)
Normal	< 120	and < 80
Pre-hypertension	120-139	or 80-89
Stage 1 hypertension	140-159	or 90-99
Stage 2 hypertension	≥ 160	or ≥ 100

Table 6 Recommendations for Follow-up Based on Initial Blood Pressure Measurements for Adults Without Acute End Organ Damage

Initial Blood Pressure (mmHg)[a]	Follow-up Recommended[b]
Normal	Recheck in 2 years
Pre-hypertension	Recheck in 1 year [c]
Stage 1 hypertension	Confirm within 2 months [c]
Stage 2 hypertension	Evaluate or refer to source of care within 1 month. For those with higher pressures (e.g. above 180/110 mmHg), evaluate and treat immediately or within 1 week depending on clinical situation and complications.

a. If systolic and diastolic categories are different, follow recommendations for shorter time follow-up (e.g. 160/86 mmHg should be evaluated or referred to source of care within 1 month)
b. Modify the scheduling of follow-up according to reliable information about past BP measurements, other cardiovascular risk factors, or target organ disease
c. Provide advice about lifestyle modifications.

APPENDIX I CONCOMITANT MEDICATIONS PROHIBITED OR TO BE USED ONLY WITH PRIOR PERMISSION

Table 7 through Table 15 provide examples of drugs that are **PROHIBITED** for concomitant use in COR-2017-OLE. Table 16 through Table 18 provide examples of drugs that **REQUIRE PERMISSION** from the study Medical Monitor prior to concomitant use.

Some drugs have been categorized into multiple drug interaction categories (e.g. dexamethasone is both a systemic corticosteroid and a strong CYP3A4 inducer). Where drugs are categorized into more than one category, the most restrictive category should hold precedent.

Although an attempt was made to provide a comprehensive list of relevant medications that are believed to present a potential risk of clinically significant drug interaction with levoketoconazole, the lists intentionally omit some medications that should not be used concomitantly with levoketoconazole, since concomitant use is not expected (e.g. some chemotherapeutic agents), and the lists probably omit others unintentionally. Furthermore, these lists will evolve as new drugs come to market and more is learned about the pharmacology of levoketoconazole and other medications. Therefore, they should be regarded as a minimum set of excluded and precautioned concomitant medications.

A. Prohibited concomitant medications

Table 7 Steroidogenesis Inhibitors and Systemic Corticosteroids

Interfere with study drug assessment; must be avoided or washed out prior to Baseline Visit

Steroidogenesis Inhibitors:	Systemic corticosteroids include any corticosteroid intended to act systemically, alone or in combination with other drugs, examples include:
Metyrapone	Betamethasone, Budesonide, Cortisone, Deflazacort,
Ketoconazole	Dexamethasone (except for DST), Hydrocortisone,
Etomidate	Methylprednisolone, Prednisolone, Prednisone,
Mitotane	Triamcinolone
Trilostane	

Table 8 Dopamine Agonists

Interfere with study drug assessment; must be avoided or washed out prior to Baseline Visit

Apomorphine	Pergolide
Bromocriptine	Piribedil
Cabergoline (8 weeks' washout)	Pramipexole
Ciladopa	Propylnorapomorphine
Dihydroergotamine/ergotamine	Quinagolide
Dihydrexidine	Ropinirole
Dinapsoline	Rotigotine
Doxanthrine	Roxindole
Epicriptine	Sumanirole
Etilevodopa (alone or with inhibitors of dopamine metabolism)	
Levodopa (alone or with inhibitors of dopamine metabolism)	
Lisuride	
Melevodopa (alone or with inhibitors of dopamine metabolism)	

Table 9 Synthetic Progestins that Bind with Moderate to High Affinity[1] to Glucocorticoid Receptor (GR) or Mineralocorticoid Receptor (MR)

Interfere with study drug assessment and/or influence underlying signs/symptoms of disease; must be avoided or washed out

Medroxyprogesterone acetate	Megestrol acetate	Micronized progesterone
Segesterone (nesterone) acetate	Drospirenone	Gestodene

Table 10 Somatostatin Analogs

Interfere with study drug assessment and/or influence underlying signs/symptoms of disease; must be avoided

Octreotide (all forms)	Lanreotide (all forms)	Pasireotide (all forms)

[1] The listed drugs have been reported to bind with at least 50% relative binding affinity to GR or MR as compared with the natural ligand (set as 100%). Africander D. et al. *Steroids* 76:636-652, 2011.

Table 11 Weight Loss Medications

Interfere with endpoints assessment; must be avoided or washed out

Amfepramone	Diethylpropion	Orlistat
Benzphetamine	Ephedrine	Phendimetrazine
Bupropion/naltrexone	Etilamfetamine	Phentermine
Buproprion	Fenfluramine	Rimonabant
Cathine	Lorcaserin	Sibutramine
Clobenzorex	Mazindol	Topiramate
Dexfenfluramine	Mefenorex	

Table 12 Drugs Predicted to Interfere with the Absorption of Levoketoconazole

Must be avoided; use an allowed substitute or washout

Histamine H2-receptor antagonists: Sucralfate, cimetidine, famotidine, nizatidine, ranitidine, **Proton-pump inhibitors:** dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole

Note on Drug-drug Interactions via CYP3A4

Levoketoconazole is a substrate and potent inhibitor of CYP3A4. Therefore, the following drug interactions may occur when levoketoconazole is co-administered with other drugs that interact with CYP3A4.

- Levoketoconazole may decrease the elimination of drugs metabolized by CYP3A4, thereby increasing their plasma concentrations. Increased exposure to these drugs may cause an increase or prolongation of their therapeutic and/or adverse effects. **Concomitant use with levoketoconazole is prohibited for drugs known to present a risk of serious side effects with increased exposure** (Table 13).
- For other drugs that are metabolized by CYP3A4, monitoring of plasma concentrations is advised when possible. Clinical signs and symptoms associated with these drugs should be monitored, with dosage adjusted as needed.
- Drugs that may significantly decrease or increase the plasma concentrations of levoketoconazole by induction or inhibition of CYP3A4 or by altering absorption are prohibited (Table 14).

The following drug interaction checker may be useful (See "Interaction View" tab). However, this checker will not supersede the protocol excluded medications lists nor the judgement of the Medical Monitor or delegate:
https://mor.nlm.nih.gov/RxNav/search?searchBy=String&searchTerm=ketoconazole

Table 13 Drugs Whose Systemic Exposure is Predicted to be Significantly Increased by Levoketoconazole via CYP3A4 Inhibition

Must be avoided or washed out

Systemic exposure to these drugs is potentially increased **significantly** by the addition of levoketoconazole**; must be avoided**	
Alprazolam, midazolam, triazolam Cisapride Dofetilide Eplerenone Ergot alkaloids (ergotamine, dihydroergotamine) Quinidine	HMG-CoA reductase inhibitors: atorvastatin, lovastatin, simvastatin, (**NOT** pravastatin, fluvastatin, pitavastatin and rosuvastatin) Pimozide Nisoldipine

Table 14 Drugs That Are Predicted to Reduce (Top) or Increase Significantly (Bottom) the Plasma Concentration of Levoketoconazole via CYP3A4 Induction or Inhibition, Respectively and Are Prohibited

Must be avoided or washed out

Strong CYP3A4 Inducers

Avasimibe	Oxcarbazepine
Carbamazepine	Phenobarbital
Enzalutamide	Phenylbutazone
Efavirenz	Phenytoin
Fosphenytoin	Pioglitazone
Griseofulvin	Rifabutin
Isoniazid	Rifampicin
Modafinil	Rifampin
Nafcillin	Rifapentine
Nelfinavir	St John's wort
Nevirapine	Sulfinpyrazone

Strong CYP3A4 Inhibitors

Atazanavir	Indinavir	Suboxone
Boceprevir	Iopinavir	Telaprevir
Ceritinib	Itraconazole	Telithromycin
Clarithromycin	Mibefradil	Telaprevir
Cobicistat & coformulations	Nefazodone	Telithromycin
Conivaptan	Ombitasvir-combinations	
Darunavir	Posaconazole	
Idelalisib	Saquinavir	

Table 15 Drugs that can Cause QTc Prolongation

Must be avoided, unless no acceptable alternative is available; permission prior to use is required

Alfuzosin	Eliglustat	Perphenazine
Amiodarone	Erythromycin	Pimozide
Anagrelide	Fingolimod	Pipamperone
Arsenic	Flecainide	Procainamide
Artemether	Fluconazole	Propafenone
Asenapine	Granisetron	Propofol
Astemizole	Haloperidol	Quetiapine
Atomoxetine	Hydrocodone ER	Quinine
Azithromycin	Ibutilide	Ranolazine
Bedaquiline	Iloperidone	Risperdone
Buprenorphine	Imipramine	Solifenacin
Chloroquine	Isradipine	Sotalol
Cilostazol	Levofloxacin	Sulpiride
Ciprofloxacin	Lopinavir	Tetrabenazine
Citalopram	Lumefantrine	Thioridazine
Clomipramine	Methadone	Tiapride
Desipramine	Mirabegron	Tizanidine
Disopyramide	Mirtazapine	Tolterodine
Dolasetron	Moexipril/HCTZ	Toremifene
Domperidone	Moxifloxacin	Trimipramine
Donepezil	Norfloxacin	Tropisetron
Dosulepin	Nortriptyline	Vardenafil
Doxepin	Ofloxacin	Venlafaxine
Dronedarone	Ondansetron	Ziprasidone
Droperidol	Paliperidone	Zuclopenthixol

B. Concomitant medications that require prior permission to be used

Table 16. Drugs Whose Systemic Exposure is Predicted to be Increased Moderately by Levoketoconazole

Systemic exposure to these drugs is predicted to be increased by levoketoconazole: Substitute if possible and discuss with Medical Monitor prior to use. Careful monitoring is recommended, with possible adjustment in doses.

Alfentanil, fentanyl, sufentanil	Docetaxel, paclitaxel
Amlodipine, felodipine, nicardipine, nifedipine	Rifabutin
Bosentan	Sildenafil
Buspirone	Sirolimus
Busulfan	Tacrolimus
Cariprazine	Telithromycin
Coumarin oral anticoagulants	Trimetrexate
Cyclosporine	Verapamil
Digoxin	Vinca alkaloids

Table 17 Topical or Inhaled Steroids (other than low potency products)

Interfere with study drug assessment; should be avoided; to be used only with prior permission

Inhaled corticosteroids:	Flunisolide
Beclomethasone	Fluticasone furoate
Betamethasone dipropionate	Mometasone
Budesonide	Prednisolone
Ciclesonide	Tixocortol
Dexamethasone	Triamcinolone
Topical/inhaled corticosteroids: Fluticasone propionate	
Topical corticosteroids:	
Amcinonide	Halcinonide
Clobetasol propionate	Halobetasol propionate
Esocimetasone	Halometasone
Diflorasone diacetate	Hydrocortisone butyrate
Fluocinolone acetonide	Hydrocortisone valerate
Fluocinonide	Mometasone furoate
Flurandrenolide	Triamcinolone acetonide

Table 18 Other Medications Contraindicated or Relatively Contraindicated with Ketoconazole

Increased risk of AEs; to be used only with prior permission

Afatinib	Ergoloid Mesylates	Nimodipine
Alitretinoin	Ergonovine	Olaparib
Almotriptan	Escitalopram	Oxycodone
Amodiaquine	Estazolam	Palbociclib
Aprepitant	Eszopiclone	Pazopanib
Aripiprazole	Everolimus	Red Yeast Rice
Artesunate	Fesoterodine	Reboxetine
Avanafil	Flibanserin	Rivaroxaban
Axitinib	Grazoprevir	Saccharomyces boulardii
Barnidipine	Ibrutinib	Salmeterol
Brexpiprazole	Pendetide	Silodosin
Blonanserin	Irinotecan	Simeprevir
Bosutinib*	Isavuconazonium Sulfate	Sonidegib
Cabozantinib	Ivabradine	Suvorexant
Cobimetinib	Lapatinib	Tamsulosin
Crizotinib	Lercanidipine	Tegafur
Cyclosporine	Levomilnacipran	Ticagrelor
Dabrafenib	Lomitapide	Tolvaptan
Dapoxetine	Lurasidone	Trabectedin
Edoxaban	Macitentan	Udenafil
Elbasvir	Methylergonovine	Ulipristal
Eletriptan	Mirodenafil	Vorapaxar
	Naloxegol	

*Examples of contraindicated tyrosine kinase inhibitors (TKIs) are shown; all approved TKIs are also contraindicated for purposes of the study.

APPENDIX J SIGNS AND SYMPTOMS OF CONDITIONS TO BE CONSIDERED FOR RISK MANAGEMENT

Disease	Symptoms	Signs	Laboratory values
Adrenal Insufficiency	Fatigue/Tiredness/Malaise Weakness Anorexia Nausea Vomiting Constipation Abdominal pain Diarrhea Headache Salt craving Arthralgias/Myalgias Dizziness (esp. on standing) **Less common:** Irritability Depression Sweating Fever	Weight loss Hypotension Hyperpigmentation **Less common:** Hypoglycemia	Serum cortisol level less than 3 µg/dL, Inadequate cortisol response to ACTH stimulation Hypoglycemia Moderate to high ACTH (assuming primary adrenal insufficiency)
Hypocortisolemia	Fatigue Muscle weakness Loss of appetite Weight loss Nausea, vomiting Dizziness, esp. on standing Irritability Depression Sweating Joint aches and pains	Low blood pressure Symptomatic Orthostatic hypotension Reduction in weight	Reduced serum and salivary cortisol levels Hypoglycemia
Hypomineralocorticoidism	Muscle weakness Fatigue Fainting Salt craving Irritability	Low blood pressure Severe orthostatic hypotension	Hyperkalemia Hyponatremia
Hypogonadism	Erectile dysfunction Reduction in beard and body hair Enlarged breasts (in men) Fatigue Reduced libido Hot flashes Difficulty concentrating	Gynecomastia Reduced body hair Osteoporosis	Reduced testosterone levels (AE in males, beneficial in women)

APPENDIX K QUALITY OF LIFE QUESTIONNAIRE

CUSHING'S SYNDROME QUALITY OF LIFE QUESTIONNAIRE

(Cushing QoL)

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

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

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

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

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

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

4. I bruise easily.

☐ Always
☐ Often
☐ Sometimes
☐ Rarely
☐ Never

5. I am more irritable, I have sudden mood swings and angry outbursts.

☐ Always
☐ Often
☐ Sometimes
☐ Rarely
☐ Never

6. I have less self-confidence, I feel more insecure.

☐ Always
☐ Often
☐ Sometimes
☐ Rarely
☐ Never

7. I'm worried about the changes in my physical appearance due to my illness.

☐ Very much
☐ Quite a bit
☐ Somewhat
☐ Very little
☐ Not at all

8. I feel less like going out or seeing relatives or friends.

☐ Always
☐ Often
☐ Sometimes
☐ Rarely
☐ Never

9. I have had to give up my social or leisure activities due to my illness.

☐ Always

☐ Often
☐ Sometimes
☐ Rarely
☐ Never

10. My illness affects my everyday activities such as working or studying.

☐ Always
☐ Often
☐ Sometimes
☐ Rarely
☐ Never

11. It's difficult for me to remember things.

☐ Always
☐ Often
☐ Sometimes
☐ Rarely
☐ Never

12. I'm worried about my health in the future.

☐ Very much
☐ Quite a bit
☐ Somewhat
☐ Very little
☐ Not at all

APPENDIX L ASSESSMENT OF CLINICAL SIGNS AND SYMPTOMS OF CUSHING'S SYNDROME

Visit ☐☐☐☐ **Date** ☐☐ ☐☐☐ ☐☐☐☐

DD MMM YYYY

SUBJECT NUMBER: ☐☐☐☐☐☐☐ **SUBJECT INITIALS:** ☐☐☐

To be completed by The Investigator

The severity of specific signs and symptoms will be rated at each visit by the Investigator on a categorical 4-point scale:

1.	**Moon facies:**	**None**	**Mild**	**Moderate**	**Severe**
2.	**Facial plethora:**	**None**	**Mild**	**Moderate**	**Severe**
3.	**Striae:**	**None**	**Mild**	**Moderate**	**Severe**
4.	**Bruising:**	**None**	**Mild**	**Moderate**	**Severe**
5.	**Supraclavicular fat:**	**None**	**Mild**	**Moderate**	**Severe**

6. Menstrual abnormalities (females only):

A. Irregular menstruation:

None Mild Moderate Severe

Definition: A disorder characterized by irregular cycle or duration of menses.
***Mild** - Intermittent menses with skipped menses for no more than 1 to 3 months*
***Moderate** – Intermittent menses with skipped menses for more than 4 to 6 months*
***Severe** - Persistent amenorrhea for more than 6 months*

B. Dysmenorrhea: **None Mild Moderate Severe**

Definition: A disorder characterized by abnormally painful abdominal cramps during menses.
***Mild** - Mild symptoms; intervention not indicated*
***Moderate** – Moderate symptoms; limiting instrumental ADL*
***Severe** - Severe symptoms; limiting self-care ADL*

In addition, the following physical signs of CS will be quantified by the Investigator using specific grading systems described below:

7. Acne (grading according to Doshi 1997)
8. Hirsutism (grading according to Hatch 1981)
9. Peripheral edema (grading according to Brodovicz 2009)

Name of Investigator completing assessment (Printed)_____

Signature of Investigator completing Assessment_____

Date_____

Grading Systems for Question 7, 8, and 9 in the Assessment of Clinical Signs and Symptoms of Cushing's Syndrome.

Acne:

Acne assessments will be performed using the Global Acne Grading System described by Doshi, et al. (1997). A total of six locations will be evaluated.

- Forehead
- Right Cheek
- Left Cheek
- Nose
- Chin
- Chest and Upper Back

Grading Scale:

0 = No lesions

1 = ≥ one comedone

2 = ≥ one papule

3= ≥ one pustule

4 = ≥ one nodule

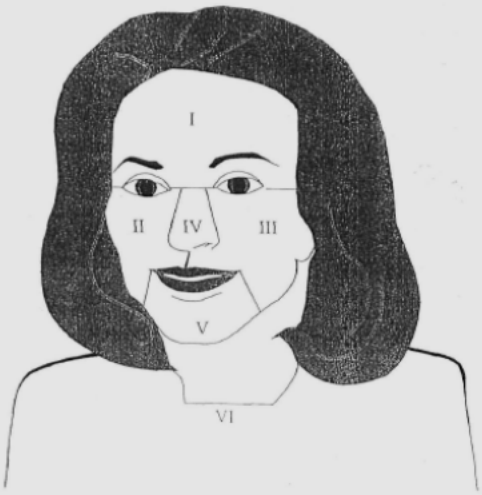

Figure 1 The six locations (I–VI) of the Global Acne Grading System (GAGS)

Evaluate each of the six locations identified above and assign a grade. Record the grading within the eCRF, which will calculate the Local and Global Scores.

Location	Grade (0-4)
Forehead (I)	
Right Cheek (II)	
Left Cheek (III)	
Nose (IV)	
Chin (V)	
Chest and Upper Back (VI)	

Hirsutism (Females Only):

Hirsutism will be evaluated using the rating system described by Hatch (1981). The degree of hairiness present will be evaluated for nine body areas:

- Upper Lip
- Chin
- Chest
- Abdominal
- Pubic
- Arm
- Thigh
- Back
- Buttocks

Grading Scale: [**NOTE:** Use grade 0 for no hirsutism]

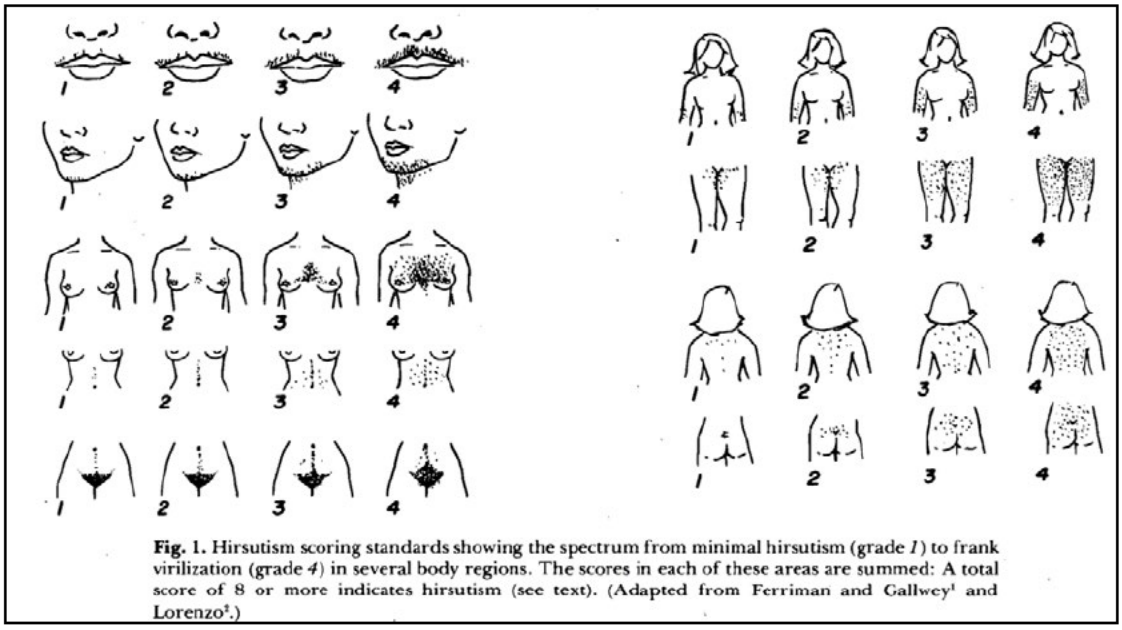

Fig. 1. Hirsutism scoring standards showing the spectrum from minimal hirsutism (grade *1*) to frank virilization (grade *4*) in several body regions. The scores in each of these areas are summed: A total score of 8 or more indicates hirsutism (see text). (Adapted from Ferriman and Gallwey[1] and Lorenzo[2].)

Evaluate each of the nine locations identified above and assign a grade. Record the grading within the eCRF.

Body Area	Rating (0-4)
Upper Lip	
Chin	
Chest	
Abdominal	
Pubic	
Arm	
Thigh	
Back	
Buttocks	

Edema:

Edema will be assessed according to the method established by Brodovicz, et al. (2009). Three anatomical areas will be evaluated:

- Lower calf at 7 cm proximal to the midpoint of the medial malleolus
- Behind the medial malleolus
- Dorsum of the foot

Each location will be individually evaluated. Using two fingers or thumb, press the skin firmly in the area to be evaluated and start the stopwatch or watch (second hand) immediately after release of pressure until completion of rebound to pre-pressure appearance.

Evaluate each of the three locations identified above and assign a grade. Record the grading within the eCRF. If there is no edema, enter 0.

Grading Scale:

Pitting Edema - measurement

1+	Barely detectable impression when finger is presssed into skin.
2+	Slight indentation. 15 seconds to rebound
3+	Deeper indentation. 30 seconds to rebound.
4+	> 30 seconds to rebound.

O'Sullivan, S.B. and Schmitz T.J. (Eds.). (2007). Physical rehabilitation: assessment and treatment (5th ed.). Philadelphia: F. A. Davis Company. p.659

Body Area	**Rating (1-4)**	**Time to Rebound (sec)**
Lower calf at 7 cm proximal to the midpoint of the medial malleolus		
Behind the medial malleolus		
Dorsum of the foot		

APPENDIX M BECK DEPRESSION INVENTORY (BDI-II)

BDI-II

Date:

Name: _____ Marital Status: _____ Age: _____ Sex: _____

Occupation: _____ Education: _____

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today.** Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness
- 0 I do not feel sad.
- 1 I feel sad much of the time.
- 2 I am sad all the time.
- 3 I am so sad or unhappy that I can't stand it.

2. Pessimism
- 0 I am not discouraged about my future.
- 1 I feel more discouraged about my future than I used to be.
- 2 I do not expect things to work out for me.
- 3 I feel my future is hopeless and will only get worse.

3. Past Failure
- 0 I do not feel like a failure.
- 1 I have failed more than I should have.
- 2 As I look back, I see a lot of failures.
- 3 I feel I am a total failure as a person.

4. Loss of Pleasure
- 0 I get as much pleasure as I ever did from the things I enjoy.
- 1 I don't enjoy things as much as I used to.
- 2 I get very little pleasure from the things I used to enjoy.
- 3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings
- 0 I don't feel particularly guilty.
- 1 I feel guilty over many things I have done or should have done.
- 2 I feel quite guilty most of the time.
- 3 I feel guilty all of the time.

6. Punishment Feelings
- 0 I don't feel I am being punished.
- 1 I feel I may be punished.
- 2 I expect to be punished.
- 3 I feel I am being punished.

7. Self-Dislike
- 0 I feel the same about myself as ever.
- 1 I have lost confidence in myself.
- 2 I am disappointed in myself.
- 3 I dislike myself.

8. Self-Criticalness
- 0 I don't criticize or blame myself more than usual.
- 1 I am more critical of myself than I used to be.
- 2 I criticize myself for all of my faults.
- 3 I blame myself for everything bad that happens.

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

10. Crying
- 0 I don't cry any more than I used to.
- 1 I cry more than I used to.
- 2 I cry over every little thing.
- 3 I feel like crying, but I can't.

_____ Subtotal Page 1 Continued on Back

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11. Agitation

0 I am no more restless or wound up than usual.
1 I feel more restless or wound up than usual.
2 I am so restless or agitated that it's hard to stay still.
3 I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

0 I have not lost interest in other people or activities.
1 I am less interested in other people or things than before.
2 I have lost most of my interest in other people or things.
3 It's hard to get interested in anything.

13. Indecisiveness

0 I make decisions about as well as ever.
1 I find it more difficult to make decisions than usual.
2 I have much greater difficulty in making decisions than I used to.
3 I have trouble making any decisions.

14. Worthlessness

0 I do not feel I am worthless.
1 I don't consider myself as worthwhile and useful as I used to.
2 I feel more worthless as compared to other people.
3 I feel utterly worthless.

15. Loss of Energy

0 I have as much energy as ever.
1 I have less energy than I used to have.
2 I don't have enough energy to do very much.
3 I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

0 I have not experienced any change in my sleeping pattern.

1a I sleep somewhat more than usual.
1b I sleep somewhat less than usual.

2a I sleep a lot more than usual.
2b I sleep a lot less than usual.

3a I sleep most of the day.
3b I wake up 1–2 hours early and can't get back to sleep.

17. Irritability

0 I am no more irritable than usual.
1 I am more irritable than usual.
2 I am much more irritable than usual.
3 I am irritable all the time.

18. Changes in Appetite

0 I have not experienced any change in my appetite.

1a My appetite is somewhat less than usual.
1b My appetite is somewhat greater than usual.

2a My appetite is much less than before.
2b My appetite is much greater than usual.

3a I have no appetite at all.
3b I crave food all the time.

19. Concentration Difficulty

0 I can concentrate as well as ever.
1 I can't concentrate as well as usual.
2 It's hard to keep my mind on anything for very long.
3 I find I can't concentrate on anything.

20. Tiredness or Fatigue

0 I am no more tired or fatigued than usual.
1 I get more tired or fatigued more easily than usual.
2 I am too tired or fatigued to do a lot of the things I used to do.
3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

_____ Subtotal Page 2

_____ Subtotal Page 1

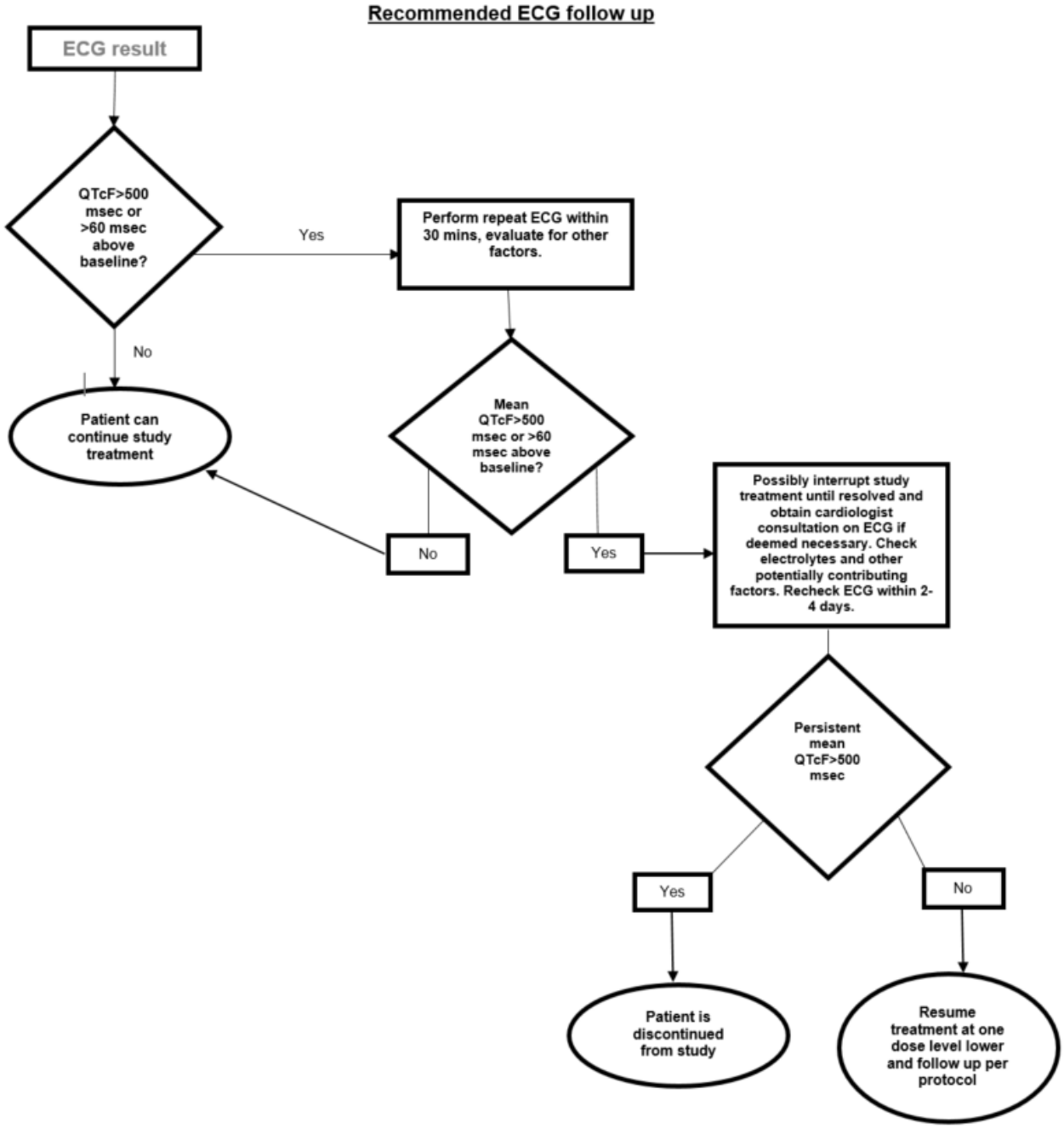
_____ Total Score

BDI-II F9542DFRM-A

APPENDIX N ADDITIONAL INFORMATION ON ADVERSE EVENTS OF SPECIAL INTEREST (QTC INTERVAL, INSTRUCTIONS FOR LIVER FUNCTION TEST ABNORMALITIES FOLLOW-UP AND ADRENAL INSUFFICIENCY)

Additional Information for QTc Interval Monitoring

In this study, ECG monitoring is recommended at least every 3 months using a 12-lead ECG. ECGs will be obtained prior to the first dose of drug in the OLE as an OLE Baseline and every 3 months after enrollment.



Additional Information for LFT evaluation

Although newly recognized LFT abnormalities will be less likely in the population for this extension study than in the parent studies, subjects will be monitored and withdrawal due to abnormal liver function tests will likewise be prompted per the criteria and evaluation procedures outlined in Sections 13.7and 14.2.

The recommendations within the FDA Guidance on Drug-Induced Liver Injury: Premarketing Clinical Evaluation (May 2009) have been adopted for use in this protocol to address abnormal LFTs. LFTs, including AST, ALT, TBN, LDH and AP, will be measured at every study visit. In addition, LFTs will be measured immediately if subjects develop signs and symptoms suggestive of hepatic dysfunction (any of the following: nausea, anorexia, fever, fatigue, right upper quadrant discomfort, pruritus, dark urine or acholic stool). **Nausea, anorexia, and fatigue are non-specific symptoms and may be caused by hypocortisolemia; however, appropriate medical evaluation of such symptoms must include assessment of LFTs.**

Testing that is performed to evaluate abnormal LFTs, including laboratory assessments to exclude confounding causes (such as, hepatitis [A, B, C, E], autoimmunity), imaging and consultation with a liver specialist should be done **prior to** planned withdrawal of subjects due to elevated LFTs, so that the etiology of the abnormalities might be determined definitively while the subject remains available for evaluation. The Medical Monitor will provide Investigators with suggested evaluation procedures as outlined in Instructions for Liver Function Test Abnormalities Follow-up below. All such evaluations and any interventions to address LFT abnormalities should be recorded in the eCRF. While LFTs may be assayed at a local laboratory for immediate medical intervention, simultaneous samples **must** be sent to the central laboratory to ensure consistency of assay and interpretation.

Evaluation of LFT Abnormalities and Study Medication Dosing Interruption

Prior to considering study withdrawal, subjects meeting the above criteria at any visit should be evaluated with serial (repeated) LFTs and potentially additional diagnostic evaluative testing to establish an etiology of the abnormality.

The first repeated LFT assay should be performed as soon as possible after initial determination of abnormality to confirm the observation and thereafter at 3- to 4-day intervals or as the clinical situation dictates. Appropriate diagnostic evaluations and interventions should be implemented based on the clinical presentation of the subject and following the instructions for AESI-LFT abnormality follow-up (Instructions for Liver Function Test Abnormalities Follow-up).

Instructions for Liver Function Test Abnormalities Follow-up

If a patient experiences a potential hepatic event, the following information will be requested.

1. Pertinent details of the patient's medical history (inclusive of alcohol use, recreational drug use, special diets, non-alcoholic steatohepatitis, and prior elevations in LFTs), with start/end dates were known.

2. Details of any recent or current use of acetaminophen/paracetamol (including cold/allergy medications containing acetaminophen/paracetamol) with start/stop dates and doses.

3. Concomitant medications (including herbal and non-prescription medications, and dietary supplements), with start/stop dates and doses.

4. Potentially confounding factors for the event.

5. Details of any symptoms present around the time of the event such as:

   Fatigue

   Nausea

   Vomiting

   Rash/pruritis

   Eosinophilia

   Dark urine

   Acholic stool

   Fever

   Right upper quadrant pain/tenderness

6. Information regarding liver specialist consultation.

7. Results of any LFTs performed to date (including Baseline and repeat testing).

8. All INR, prothrombin time (PT) and prothromboplastin time (PTT) readings (NOTE: coagulation tests are not routinely performed in this study but should be performed and followed if abnormal in the event of suspected liver injury).

9. Imaging procedures.

10. Any other tests performed (liver panel below can be ordered from central laboratory).

    Hepatitis A Antibody, immunoglobulin M (Focus)

    Hepatitis B Core IgM AB (Centaur)

    Hepatitis B Virus DNA Quant polymerase chain reaction (Panel)

    Hepatitis D Antibody, Total

    Hepatitis E Ab IgM

    Cytomegalovirus IgM Antibody

    Epstein-Barr Viral Capsid Antigen IgM Antibody (Focus)

    Acetaminophen Adduct

Actin (Smooth Muscle) Antibody

ANA screen with reflex

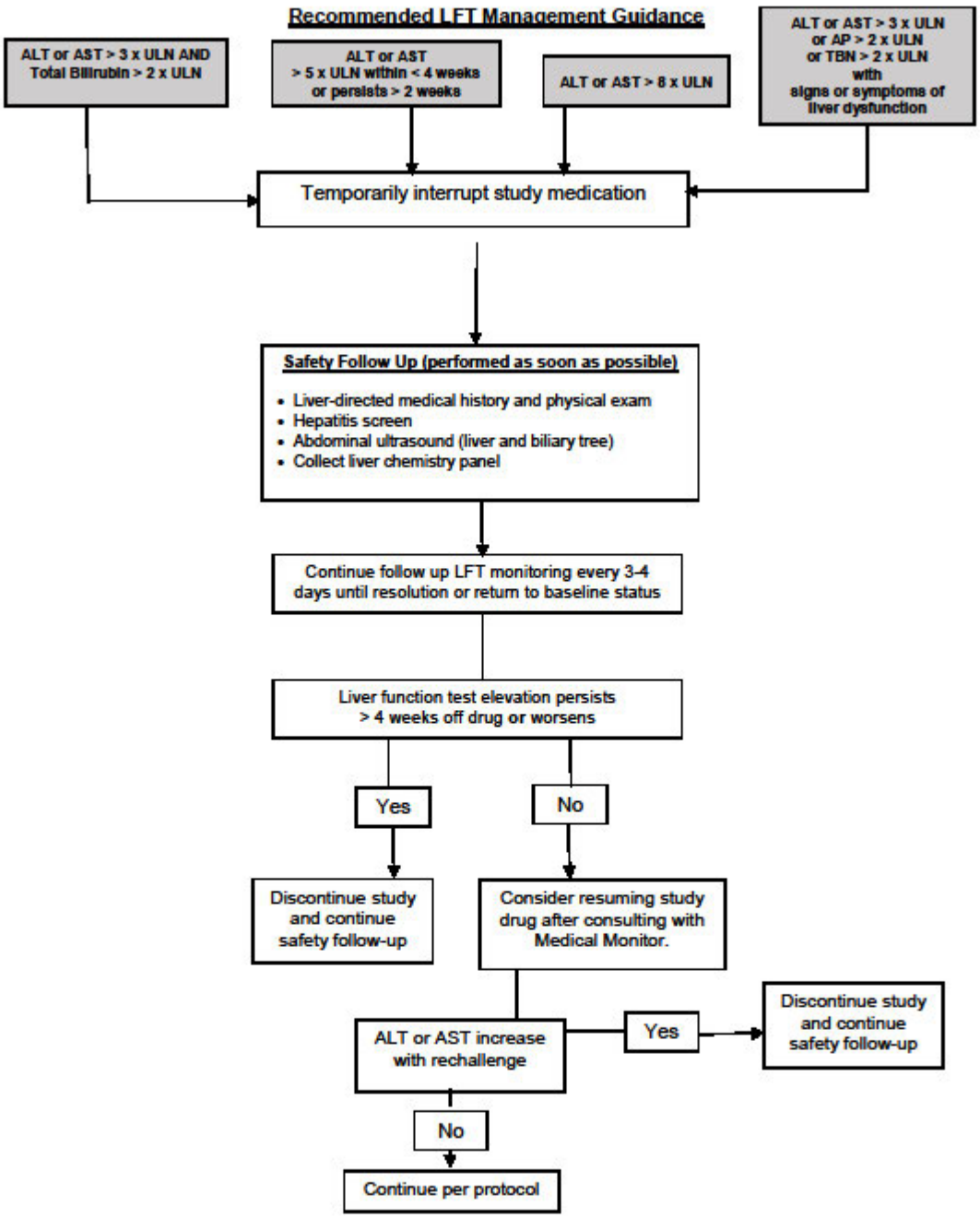
ANA screen with reflex to titer and pattern (Panel)-Bioplex

Immunoglobulin G (IgG)

Liver Kidney Microsome-1 Antibody

Ammonia

11. Dechallenge and rechallenge results.


Recommended LFT Management Guidance
ALT or AST > 3 x ULN AND Total Bilirubin > 2 x ULN
ALT or AST > 5 x ULN within < 4 weeks or persists > 2 weeks
ALT or AST > 8 x ULN
ALT or AST > 3 x ULN or AP > 2 x ULN or TBN > 2 x ULN with signs or symptoms of liver dysfunction
Temporarily interrupt study medication
Safety Follow Up (performed as soon as possible)
• Liver-directed medical history and physical exam
• Hepatitis screen
• Abdominal ultrasound (liver and biliary tree)
• Collect liver chemistry panel
Continue follow up LFT monitoring every 3-4 days until resolution or return to baseline status
Liver function test elevation persists > 4 weeks off drug or worsens
Yes
No
Discontinue study and continue safety follow-up
Consider resuming study drug after consulting with Medical Monitor.
ALT or AST increase with rechallenge
Yes
Discontinue study and continue safety follow-up
No
Continue per protocol

Algorithm for Management of Adrenal Insufficiency