CORTENDO

CLINICAL STUDY PROTOCOL

A Double-blind, Placebo-Controlled, Randomized Withdrawal Following Open-label Therapy Study to Assess the Safety and Efficacy of Levoketoconazole (2S, 4R-ketoconazole) in the Treatment of Endogenous Cushing's Syndrome

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Compound	Levoketoconazole
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Phase	3
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Amendment 4	23 September 2019
Amendment 3	14 December 2018
Amendment 2	21 June 2018
Amendment 1	06 July 2017
Original	17 April 2017
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Revision Chronology

Version	Date
Final	17 April 2017
Amendment 1: • Throughout, clarified and corrected references to the visits in Randomized Withdrawal Phase: RW1 is the second visit of the Randomized Withdrawal Phase and is the first time when loss of prior-established UFC response is assessed. Removed exploratory endpoint 'Changes from Baseline (RW0) in late night salivary cortisol (LNSC) at all post-Baseline visits with these assessments through the final study visit (RES2)', as this endpoint is included as the secondary endpoint 'Changes from Baseline (RW0) in mean urinary free cortisol (mUFC) and LNSC at all post-Baseline visits with these assessments through the final study visit (RES2)'. • Clarified method of planned statistical analysis for primary endpoint and added additional details of planned statistical analyses for primary and secondary endpoints in synopsis. • Standardized definition of relapse throughout to match definition in Section 3.1. • Revised planned target population to comprise approximately one-half SONICS completers and one-half levoketoconazole-naïve (rather than two-thirds and one-third as previously planned) and increased the maximum proportion of levoketoconazole-naïve subjects to 70%, if needed. • Clarified subject categorization of prior levoketoconazole use. Clarified screening and RW0 procedures for subjects who have exited SONICS more than six months prior to the Screening Phase and have been on a stable Therapeutic Dose throughout the previous 12-week period. • Inclusion criteria for all others: Corrected the dexamethasone value required. • Exclusion criteria: Added a criterion for subjects enrolled in SONICS who did not complete SONICS through Visit M12; removed the need for central reading of electrocardiogram (ECG) for Screening determination of eligibility; added alkaline phosphatase (AP) above 2X upper limit of normal (ULN) as grounds for exclusion; removed specification of uncontrolled hypertension (180/120 mmHg). • Clarified throughout that members of SONICS-Completer cohort must have maintained treatment with a Therapeutic Dose of levoketoconazole for a minimum of 12 weeks prior to screening. • Clarified that an Open Label Extension (OLE) study is being planned for qualifying participants in the current study. • Clarified that the Signs and Symptoms of Cushing's Syndrome can also be performed by a qualified home healthcare professional with training. Specified that the person completing the Signs and Symptoms of Cushing's assessments should, when possible, remain consistent for individual subjects. Specified that, in cases of clinically significant deterioration of clinical signs and symptoms of CS, home healthcare professionals should refer the subject back to the physician for corroboration prior to initiation of early rescue therapy.	06 July 2017

• Removed descriptor of pharmacokinetic (PK) Sample Collection as applying only to Levoketoconazole-naïve and re-titrations only. Removed PK sampling from visits TM1, RW0 and RES2. Corrected inconsistency of PK requirement at TM7. Clarified that PK samples collected at hours 6 to 8 post-dose will be collected at a different visit (TM2-TM6) than the other PK samples. • Added instructions for SONICS-completers who require re-titration to Dosage and Administration section. • Clarified that additional safety visits were to occur for subjects receiving a total daily dose of 750 mg and above. • Removed requirement 'and without evidence of cholestasis' from grounds for discontinuation of investigational therapy in the case of: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) above 3X ULN **and** total bilirubin (TBN) above 2X ULN or International Normalized Ratio (INR) above 1.5 not explained by any other cause such as viral hepatitis. • Added section describing withdrawal due to adrenal insufficiency. • Clarified that approximately 3 minutes was to elapse between triplicate heart rate measurements. • Added gamma-glutamyl transpeptidase (GGT) to panel of liver safety monitoring tests. • Corrected spelling of levonorgestrel. • Revised and clarified section on pituitary magnetic resonance imaging (MRI). • Corrected visit corresponding to dose escalation for the 750-mg dose level to TM3 (not TM4) and revised subsequent visits cited accordingly. • Clarified that when adrenal insufficiency is observed at Dose Level 1 (DL1), subjects may be provided a lower dose of 150 mg QD (Dose Level [DL] 0) following agreement with the Sponsor. Subjects may resume the Dose Titration scheme after a dose reduction at the discretion of the Investigator and agreement of the Sponsor. • Added prohibition of donation of blood or blood products during the study. • Added that the total final tablet count (active + placebo) during Restoration Phase will equal twice the total tablet count of the Therapeutic Dose, not to exceed 8 tablets twice daily (BID). • Added further details to dosage administration section 'For levoketoconazole-naïve subjects, the total daily dose will be titrated in 150 mg increments from a starting dose of 300 mg (dosed as 150 mg BID) up to a maximal daily dose of 1200 mg (dosed as 600 mg BID) until a Therapeutic Dose is established. The minimum daily dose is 150 mg once daily (QD) for subjects who cannot tolerate 150 mg BID. For subjects in the SONICS-completers cohort, the Therapeutic Dose will have been established prior to enrollment in this study. For levoketoconazole-naïve subjects, the Therapeutic Dose will be established by the end of the Dose Titration / Maintenance Phase. The Therapeutic Dose will be used as the target dose and dose-regimen during the Restoration Phase.' • Clarified that subjects who must re-establish their Therapeutic Dose via re-titration (at the outset of the study) may begin re-titration at their current or most	

recently received dose at the discretion of the Investigator, rather than start at DL1. • Clarified that potassium supplements are encouraged to maintain serum potassium levels within the normal range and above 4.0 mmol/L, which may reduce the risk of drug-induced QT interval (QTc) prolongation. • Clarified that timing of the first bi-annual Data Safety Monitoring Board (DSMB) meeting may be adjusted based on subject accrual. Removed the requirement for the DSMB charter to be executed prior to study initiation. • Added criterion to oral glucose tolerance test (OGTT) and Impaired fasting glucose (IFG) (≥ 100 mg/dL (5.6 mmol/L) and < 126 mg/dL (7.0 mmol/L), respectively. • Clarified that changes of pituitary tumor will be summarized from Screening to Visits RW0 and RW5 (for the levoketoconazole-naïve cohort) and from Visit RW0 to RW5 (for the SONICS-completers cohort). • Clarified the statistical analyses of clinical signs and symptoms. • Corrected definition of prediabetic subjects from 'above 100 mg/dL' to 'greater than or equal to 100 mg/dL'. • Clarified the definition of AESI of persistent QTc prolongation. • Clarified the definitions for adverse events (AEs) considered unrelated and unlikely related to study drug. • Time and events schedule: Table 8 added row for OGTT, removed MRI row, removed optional PK sampling at TM1, and made sampling at TM7 non-optional, added clarification footnotes regarding 24-h UFC/free cortisol/creatinine/ urinary volume (three collections) and that in case of AESI, a PK sample should be obtained as close to the time of the event as possible. • Time and events schedule: Table 9 removed PK sampling from RW0 and RES2 but added footnote that that in case of AESI, a PK sample should be obtained as close to the time of the event as possible. Footnotes edited for clarity. • Appendix B added salivary cortisol and dexamethasone for completeness.	
Amendment 2: • Updated typographical errors. • Corrected the date of Amendment 1 in the Summary of Changes from 22 June 17 to 06 July 2017. • Updates made to ensure consistency of wording and alignment of information between Protocol Synopsis and Protocol. • Corrected the changes in biomarkers of CS comorbidities list in the secondary objectives (Synopsis and Section 2.2), and Secondary Efficacy Analysis (Synopsis and Section 12.5.3.2) to be a consistent listing of biomarkers. • Changed condition 2 of the Primary Endpoint in the Synopsis and Sections 3.1, 3.4, as well as related footnotes, from "at or above the ULN (i.e. ≥ 1.0X ULN)" to "above the ULN (i.e. >1.0X ULN)." • Changed condition 2 of the Primary Efficacy Analysis in the Synopsis and Sections 12.5.3.1 and 12.5.3.3 from "was at least 1.0X ULN" to "is above ULN (i.e. >1.0X ULN)."	21 June 2018

• Changed condition 2 Partial loss of cortisol response from "below 1.5X ULN" to "no more than 1.5X ULN" in Early Rescue Criteria in the Synopsis and Section 4.3.1. • Removed the phrase "necessitating open-label therapy" or "necessitating open-label therapy to treat hypercortisolism" from condition 3 of the Primary Endpoint for early rescue in Synopsis and Sections 3.1, 3.4, 12.2, 12.5.3.1 and 12.5.3.3. • Added clarifying text in Synopsis and Section 4.2.2.1 for selected group of subjects who completed Visit M12 in SONICS either within 6 months or more than 6 months prior to the Screening Phase and not on a stable Therapeutic dose throughout the previous 12-week period. Procedures for these subjects should mimic those of the levoketoconazole-naïve subjects. • Added clarifying text to Appendix A Table 7 for subjects who completed SONICS more than 6 months prior to the Screening Phase and have been on stable Therapeutic Dose to mimic Screening Procedures of the levoketoconazole-naïve subjects. • Corrected the time to first normalization in Exploratory Endpoints beginning from "RES1" to "RW5" in the Synopsis and Section 3.4. Removed from Section 12.5.3.2. • Corrected the statement in the Primary Endpoint in the Synopsis and in Section 3.1 from "…from of three 24-hour UFC measurements…". to read "…from three 24-hour UFC measurements…". • Revised text and definitions throughout protocol in regard to screening procedures to ensure alignment with Appendix A Table 7. • Added clarification that the DST is not needed at screening for subjects on levoketoconazole in Section 6.4.5.3 and Appendix A Table 7. • Added clarification of OGTT test timing and definition of whom should have the test performed in Appendix A Tables 8 and 9 footnotes. • Changed the population definition for the OGTT test from "non-diabetic" to "pre-diabetic" in Appendix A Tables 8 and 9, and in the Other analytes/measures section of Appendix B Laboratory Analytes. • Updated wording throughout associated with the Dose Titration at Total Daily Doses of 750 mg or above and the need for additional safety visits in the Dose Titration and Maintenance Phase from "750 mg or higher" or "750 mg and above" or "beyond 600mg/day" or "exceeds 600 mg" or "beginning with 750 mg" or "above 600 mg/day to "750 mg/day or above" in the Synopsis and Sections 4.2.2.2, 4.2.2.4, 6.4.6.1, 6.5.2, 9.4, and Appendix A Table 8 footnotes. Removed the phrase "above 600 mg/day" when referring to additional safety visit necessary for certain dose escalations in Sections 4.2.2.4. • Added the timing of tablet count increase increments during the Restoration Phase titration beginning at RW5 will be "alternating AM and PM per Table 2 Dosing Titration Scheme" in Section 4.4, and "alternating AM and PM" in the Synopsis. • Clarified that the DSMB will be assessing "key" safety data in the Synopsis. • Added statements that "Any subject who withdraws after randomization will not be replaced" and "Withdrawn subjects will not be re-entered into the study", and	

clarified the null and alternative hypotheses definitions and sample size determination in the Synopsis and Section 12.2.1. • Clarified instrument for measurement of QTc interval in Exclusion 11 in the Synopsis to be consistent with Section 5.3. • Updated to include additional safety visits for subjects currently on levoketoconazole requiring re-titrating after TM0 through TM2, dependent on dose escalations in Section 9.3 and Appendix A Table 8. • Changed Exclusion Criteria 21 serum potassium measurement from "below 3.0 mEq/L" to "below 4.0 mEq/L" in the Synopsis, and Section 5.3. • Updated the SONICS enrollment from "is planned to enroll 90" to "enrolled 94" in Section 1.1. • Changed the most recent meeting date of the DSMB in Section 1.1 from "October 2016" to "April 2018" and changed "approximately two thirds of the study enrolled" to "the study fully enrolled". • Clarified durability of efficacy in Section 1.2. • Removed footnote in Inclusion Criteria for All Others #5 in the Synopsis and added text as a note within the Inclusion Criteria for All Others #5 in the Synopsis to be in line with Section 5.2. • Added a note to Inclusion Criteria for All others #4 and #5 in the Synopsis and in Section 5.2 to clarify that these two criteria do not apply to subjects currently on levoketoconazole. • Alignment of footnote for condition 2 of the Primary Endpoint throughout protocol. • Clarified timing for rest period prior to ECG measurement in 12-Lead ECG Section 6.4.3 from "at least 1 minute" to "at least 5 minutes". • Information added to Blinding Section 8.3.3.1 to account for top line analysis. Also clarified use of open-label levoketoconazole for subjects who require early rescue. • Added Section 12.6 Interim Analyses and Data Monitoring to the Data Analysis and Statistical Considerations section. • Added statement that "Drug accountability will not be performed during visits by HHC professional" in Section 9.3 and statement that "Drug accountability and dispensation only to be completed when visits are performed in-clinic and not applicable to HHC visits" to Appendix A Table 9. • Clarified collection of working shift and sleep hours in Lifestyle and Dietary Restrictions Section 7. • Clarified the subject population definitions (Intent-to-Treat, Per-Protocol, Levoketoconazole-naïve, and SONICS-completer) in the Analysis Populations / Populations for Analysis sections in the Synopsis and Section 12.1, respectively. • Clarified Definitions of Baseline for some endpoints analyzed during the Restoration Phase only in section 12.5.1. • Added "TEAEs of special interest" to the Adverse Events in Section 12.5.2.2. • Changed the reference from "Hotline" to "Contact Details" and "24 Hour Phone" to "24-Hour Call Center Phone" in SAE reporting Section 13.7.	

• Changed RW5 marked the start of the "Rescue Phase" to RW5 marked the start of the "Restoration Phase" in the Synopsis and Section 4.1. • Clarified statistical terminology and corrected text pertaining to statistical tests throughout protocol and in the Data Analysis and Statistical Considerations in Synopsis and Section 12. • Changed "lost UFC response" to "lost (lose/loss of) therapeutic response" in the Synopsis and Sections 12.2.1 and 12.4. • Added additional clarification to the rules to be applied when determining loss of therapeutic response when some or all mUFC data are missing in Section 12.4. • Clarified the Time to Event Analysis Section 12.5.3.3 to be in alignment with statistical terminology and Exploratory Endpoints section. • Moved UFC and LNSC Analyses-Partial loss of response section and Time to Event Analysis section, Cushing's Syndrome Quality of Life Questionnaire, and Beck's Depression Questionnaire sections from the Secondary Efficacy Section 12.5.3.2 to the Exploratory Efficacy Section 12.5.3.3. • Changed the header in Section 9.2 to refer to drug as "Investigational Product" rather than "Product" to ensure consistency throughout the section. • Added the active medication/open-label levoketoconazole drug source for subjects rolling over from SONICS and for subjects entering from EAP in Section 4.1 and in Appendix A Table 7. • Added line item in Appendix A Table 7 to "Dispense study medication/diary" during Screening for subjects who completed SONICS within the previous 6 months and currently receiving levoketoconazole. • Updated and added applicable footnotes to clarify text and ensure consistency between protocol body and Appendix A Tables 7, 8 and 9. • Renumbered and reordered footnotes throughout Appendix A Tables 7, 8, and 9. • Removed 'SONICS-completers cohort' and 'Levoketoconazole-naïve cohort' and updated descriptors in the column headers in Appendix A Table 7. • Clarified SONICS-completers (subjects who completed SONICS) versus SONICS-completers 'cohort' throughout the protocol. • Clarified that data may overlap between SONICS and LOGICS in the Synopsis and Sections 4.2.1 and 6.1. • Clarified subjects in levoketoconazole-naïve cohort "must" have their Therapeutic Dose established by end of Dose Titration and Maintenance Phase in Section 8.3.2. • Clarified subjects in SONICS-completers cohort will have their Therapeutic Dose confirmed at screening (prior to randomization) in Sections 8.3 and 8.3.2. • Clarified timing of UFCs to indicate collections must be collected prior to visits in the Dose Titration and Maintenance Phase in the Synopsis, Sections 4.2.2.2., 4.2.2.2.1, 4.2.2.2.2, and 6.4.5.1, and Appendix A Table 8. • Clarified washout must be prior to Baseline Assessments, including UFCs and LNSCs in Synopsis, Sections 4.2.2.1, 6.2, and Appendix J Table 12. • Added that urine volume can be measure by HHC professional in Section 6.4.5.1. • Clarified timing of UFC to indicate collections must be collected prior to the visit in the Randomized Withdrawal and Restoration Phases in Appendix A Table 9.	

• Clarified timing of LNSC to indicate collections must be collected before the visit in the Dose Titration and Maintenance, Randomized Withdrawal, and Restoration Phases in Section 6.4.5.2 and Appendix A Tables 8 and 9. • Added additional details for the use of SONICS M12 UFC and LNSC collection samples and required additional collections for LOGICS screening for subjects rolling over from SONICS in Sections 6.4.5.1 and 6.4.5.2 and Appendix A Table 7. • Clarified MRI procedures need to be completed if not previously done within 6 months for "TM0" to "TM0 or RW0" in the Synopsis, Section 4.2.2.1, 6.4.5.5, and Appendix A Tables 7 and 8. • Added SONICS M12 MRI may be used in Section 6.4.5.5 to ensure consistency with Appendix A Table 9. • For use of Local ECG machines in Appendix A Tables 7, 8, and 9; removed "not operational" or "unavailable" and clarified text to read "…non-operational. Local ECGs must be transmitted to Spaulding for central reading via printout." • Added Ammonia to list of other laboratory tests for Liver Panel in Appendix O. • Added Lactate Dehydrogenase (LDH) to the list of abbreviations, list of laboratory tests for Liver Safety Tests in Section 6.3, Section 6.4.4, and Appendix B. • Added details for grading and evaluating criteria for acne, hirsutism (females only) and peripheral edema to Appendix M. • Updated language in Appendix M to include the Assessment of Clinical Signs and Symptoms of Cushing's Syndrome can be completed by qualified trained HHC professional, in addition to the Investigator. • Modified line item for "Administer/dispense drug/drug accountability/patient diary" in Appendix A Table 8 to 2 separate line items "Administer Study drug/patient study diary review" and "Drug accountability/dispensation of drug and study diary" to clarify that drug accountability and dispensation of drug and study diary will not occur at additional safety visits. • Modified line item for "Administer/dispense drug/drug accountability/patient diary" in Appendix A Table 9 to 2 separate line items "Administer study drug/ patient diary review and dispensation" and "Drug accountability/dispensation of drug" to clarify activities to be performed in clinic versus during HHC visit. • Added a new visit column in Appendix A Table 8 for "Additional safety visit (HHC)" and added the caveat "(in office)" to the existing Additional safety visit column to distinguish procedures that should be completed by HHC during the Dose Titration and Maintenance Phase. • Clarified text referring to concomitant drugs that are categorized into multiple categories and added text that the restrictions of the "most restrictive" category should hold precedent in Appendix J. • Removed the duplicate medications (Buproprion and Phentermine) from Appendix J Table 16. • Changed the reference noted in Appendix J for the drug interaction checker to be used for Drug-drug interactions via CYP3A4. • Updated "unless no suitable alternative is available *after the Baseline Visit*" in	

Appendix J Table 20. • Added "Polycystic Ovary Disease (PCOD)" to the list of clinical features of CS and moved "Glucocorticoid resistance" from the clinical features list to the Unlikely to have any clinical features of CS list in Appendix G. • Replaced Appendix O "Instructions for Liver Function Test Abnormalities Follow-up" with "Additional Information on Adverse Event of Special Interest (QTc Interval, Instructions for Liver Function Test Abnormalities Follow-up and Adrenal Insufficiency)" and added additional information schematics and instructions. • Added additional references to Appendix O in the body of the Protocol. • Removed +3-day window from collection of LNSC and UFC collection for Baseline measurements in Sections 6.2, 6.4.5.2, and Appendix A Table 8. • Clarified RW0 may occur concurrently with TM7 or no more than 11 (+3 days) later unless a dose change is required at TM7 in Section 6.2 and Appendix A Table 9. • Clarified expected creatinine excretion rates in Section 6.4.5.1 and Table 4.	
Amendment 3: • 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. • Aligned use of terminology throughout the Protocol referencing the Dose Titration and Maintenance Phase to TM Phase for consistency. • Removed abbreviation for total bilirubin (TBN) and clarified instances where bilirubin should have been used instead of total bilirubin in Protocol Synopsis, Protocol and Appendices. • Increased target number of subjects for randomization to 54 with 27 in each treatment group, removed the reference to the target number of completing subjects and changed the reference to the number of anticipated SONICS-completers to represent a minority of randomized subjects in the Synopsis and Section 12.2.1. • The secondary and exploratory objectives and endpoints have been realigned and clarified. Only acne, hirsutism and peripheral edema as clinical signs and symptoms of CS have remained secondary; the other signs and symptoms have been shifted from secondary to exploratory objectives and endpoints. The health-related quality of life and symptoms of depression have been shifted from exploratory to secondary objectives and endpoints. The evaluation criteria for exploratory endpoint #2 for time from RW0 to first time of loss of response has been more clearly defined. These changes have been made in the Synopsis and the corresponding sections for objectives (Section 2.2 and Section 2.3), endpoints (Section 3.2 and Section 3.3), and efficacy analyses (Section 12.5.3.2 and Section 12.5.3.3). • Blood pressure and high-density lipoprotein cholesterol (HDL-C) have been removed from secondary objectives, endpoints and the related analysis. These	14 Dec 2018

changes have been made in the Synopsis and the corresponding sections for objectives (Section 2.2), endpoints (Section 3.2), and efficacy analyses (Section 12.5.3.2). • Clarified that subjects on levoketoconazole from SONICS or the Expanded Access Program must have confirmation of their Therapeutic Dose, as defined in the SONICS protocol, during the Screening Phase to confirm cohort placement for LOGICS in the Synopsis and Section 4.2.1. • Added clarification describing the eligibility of subjects who complete SONICS, including the Follow-up Visit in Section 4.2.2.1. The potential to use select data from the SONICS Follow-up Visit for the LOGICS Screening Visit is also described. • Clarified that eligibility for entering the Randomized Withdrawal Phase requires levoketoconazole-naïve cohort subjects to have established and maintained a Therapeutic Dose for at least 4 weeks as confirmed by the average of 3 UFC values with results received prior to the RW0 Visit in Section 4.2.2.5. • Clarified throughout the document that the TM Phase is open-label and that once the Therapeutic Dose is achieved, the dose should generally not be further adjusted if the mean UFC levels are within normal limits. However, the dose may be increased if medically necessary to maintain eucortisolemia or decreased if needed to address drug intolerance or AE. Updates were made in the Synopsis and Section 4.2.2. Section 8.3.2.1 was added to include this information. • Clarified that subjects who completed SONICS but are being treated as part of the levoketoconazole-naïve cohort must re-establish their Therapeutic Dose according to the LOGICS definition in Section 4.1. • Clarified the definition of a stable Therapeutic Dose for the SONICS-completers cohort in Section 4.1. • Clarified that subjects are not permitted a dose change during the Restoration Phase. They should be withdrawn from LOGICS owing to “loss of efficacy” and may be considered for enrollment in the OPTICS study or EAP program in the Synopsis and Section 4.4. • Clarified that subjects withdrawn due to suspected or confirmed drug-induced liver injury will not be eligible to enroll in either the OPTICS study or EAP program in Section 5.4.2. • Clarified that subjects who require early rescue during the Randomized Withdrawal Phase, may receive open-label levoketoconazole and continue in the study. The rapid titration of the Restoration Phase should be used to reestablish the Therapeutic Dose of open-label levoketoconazole used for the early rescue. Dose adjustments may be made, as medically indicated including adjustments to dose levels above the previous therapeutic dose to return subjects to eucortisolemia. Updates were made in the Synopsis, Section 4.1, Section 4.3.1, and Section 8.3.3.1. Section 8.3.3.3 was added to include this guidance information. • Clarified that subjects who may require lipid lowering drugs, they should be added and stabilized for at least 4 weeks prior to TM0 for the levoketoconazole-naïve cohort or RW0 for the SONICS-completers cohort in Exclusion Criterion #24 in the Synopsis and Section 5.3, and in Sections 10.1 and 10.2.	

• Clarified that at TM7, subjects may require more than 14 (± 3) days between TM7 and RW0 to allow for 4 weeks maintenance if a dose change is required at TM7 in the Synopsis and Section 4.2.2.2. • Added clarification that blinding to the treatment code should be maintained during early rescue in Section 4.3.1 and Section 8.3.3.1. • Added study number and name of the open-label extension (OLE) study (Study COR-2017-OLE, aka OPTICS). • Added clarification that procedures for LOGICS can only be performed during SONICS Visit M12 after the informed consent for LOGICS has been signed in Section 6.4.5.1 and Section 6.4.5.2. • Added clarification that subjects should remain awake within 2 hours before collecting the late-night salivary cortisol samples in Section 6.4.5.2. • Added clarification of information about the SONICS-completers cohort for subjects that finished SONICS within 6 months prior to screening for LOGICS and for those subjects who completed SONICS more than 6 months prior to the Screening Phase in Section 4.2.1. • Clarified in Figure 1 and in the Synopsis that during the screening period for subjects that are SONICS-completers IP may be dispensed starting at TM0 (from LOGICS for those entering Screening directly from the SONICS study and from EAP for those entering Screening directly from the EAP program). • Study Hypothesis and Sample Size Determination information was updated to align with new assumption that approximately 20% of subjects in each treatment group will withdraw prior to RW4 and to decrease the assumption of loss of response to 10% in the levoketoconazole arm in the Synopsis and Section 12.2.1. • For the Primary Efficacy Analysis, Loss of Therapeutic Response definition, the null hypothesis definitions were removed in Section 12.5.3.1. • Synopsis Screening Phase wording was clarified to remove the word ‘blood’ to align with Section 4.2.2 and Section 6.2 regarding the washout of medications that are known to influence cortisol. • Added a heading for Eligibility and included statement clarifying that Cortendo will review each subject’s enrollment criteria in the Synopsis. • Included information in Section 4.2.2.2 and Synopsis to allow for subjects still in the TM Phase when the randomization target of 54 subjects has been reached to be offered the opportunity to join the OPTICS study and receive open-label treatment provided they meet the OPTICS inclusion/exclusion criteria. • Included information in Section 4.3 that eligibility for entering the Randomized Withdrawal Phase requires subjects to have established and maintained a Therapeutic Dose as confirmed by the average of 3 UFC values with results received prior to the RW0 visit. • Clarified that the interactive randomization system is via interactive response technology (IRT) in Section 8.3.3.1. • Clarified that the duration of vital signs described in Section 6.4.2 was to occur over approximately 10 minutes.	

• Updated Appendix B to classify fasting glucose and insulin as a CS cardiovascular co-morbidity biomarker and updated Appendix A tables (Table 7, Table 8, and Table 9) to include these tests as a unique laboratory assessment. • Clarified that for urine collections between RW5 and RES1, subjects should have received the previously achieved Therapeutic Dose of blinded study medication for at least 1 week before collections commence and complete and at least 1 week before the RES1 visit. And for urine collections between RES1 and RES2, urine collection should commence at approximately Day 18 of the Restoration Phase. These updates were made in Section 6.4.5.1 and Appendix A, Table 9. • Clarified Appendix A, Table 7 to match flowchart including providing a diary to subjects who were either levoketoconazole naïve or those who completed SONICS > 6 months prior to study entry. • Clarified Appendix A, Table 9 drug accountability and dispensation to include guidance on collection of information in IRT. • Clarified Section 6.4.5.5 and Appendix A, Table 9, Footnote 13 to include guidance that the MRI for RW0 and RW5 may be performed up to 2 weeks BEFORE the study visit. • Clarified Appendix M to allow for signature by assessor. • Clarified Appendix O, Recommended LFT Management Guidance algorithm where ALT or AST > 3X ULN or AP > 2X ULN or Total Bilirubin >2X ULN to be present "with" signs or symptoms of liver dysfunction and removed reference to Appendix O.	
Amendment 4: • 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. • Clarification of the term "SONICS-completer". "SONICS-completer Cohort" is the current term used for the subset of subjects who completed the SONICS study and met the description of the cohort as provided in Section 4.1. These updates were made in the following sections: Synopsis (Eligibility, Methodology, Number of subjects, Inclusion Criteria, Investigational product, Statistical Methods); Section 2.1; Sections 4.1, 4.2.1, 4.3 and 4.3.1; Sections 5.1 and 5.3; Sections 6, 6.2, 6.3, 6.4.4.1, and 6.4.5.5; Sections 8.3 and 8.3.2; Section 10.1; Sections 12.1, 12.5.1, 12.5.2, and 12.5.3; and Appendix A. • Clarification regarding expansion of time to achieve Therapeutic Dose in levoketoconazole-naïve subjects in the Dose Titration and Maintenance Phase. This change is reflected in the following sections: Synopsis (Methodology, Dose Titration and Maintenance Phase [TM] Phase; Duration of treatment); Section 4.2.2.2; Section 4.2.2.2.2; and Section 6.2. • Clarification and updated wording on the number of potential randomized subjects and sample size determination. The updated text provides a range of target sample sizes from 46 to 54 that are dependent on the withdrawal rate prior to RW4 during the Randomized Withdrawal Phase. The following sections are	23 Sep 2019

impacted by this change: Synopsis (Methodology, Dose Titration and Maintenance [TM] Phase; Number of subjects (planned); and Study Hypothesis and Sample Size Determination); Section 4.2.2.2; and Section 12.2.1. • Addition of one secondary endpoint that addressed the proportion of subjects with normalized mUFC at the end of the Randomized Withdrawal Phase. This change applies to the following sections: Synopsis (Criteria for evaluation) and Section 3.2. The planned analysis of this endpoint has been added to Section 12.5.3.2. • Addition of two exploratory endpoints to analyze normalization rate of mUFC at TM7 and the rate of normalized mUFC or partial response at TM7. These changes apply to the following sections: Synopsis (Criteria for evaluation) and Section 3.4. The planned analyses of these endpoints have been added to Section 12.5.3.3. • Addition of eligibility of non-responders in the Dose Titration and Maintenance Phase to enroll in OPTICS. This change applies to Section 4.2.2.2. • Clarification of procedures for subjects requiring early rescue with open-label levoketoconazole during the Randomized Withdrawal Phase. This change applies to Synopsis (Methodology, Safety monitoring and extended assessment) and Section 4.3. 1. • Clarification of Early Rescue Criterion 1 (second bullet point). This change applies to Section 4.3.1. • Clarification of Early Rescue Criterion 2 (Partial loss of cortisol response). A subject must have a partial loss of cortisol response and clinically significant worsening of CS symptoms to meet this criterion. This change applies to Section 4.3.1. • Clarification regarding the abnormal dexamethasone suppression test (DST) values required for study inclusion for those subjects who had not previously completed the SONICS Study. The following sections are impacted by this change: Synopsis (Inclusion Criteria for All Others) and Section 5.2. • Additions to the study withdrawal criteria to include failure to achieve the Therapeutic Dose during the TM Phase and closure of randomization while still in the TM Phase. These changes impact Section 5.4. • Clarification regarding adequacy of urine samples. This change impacts Section 6.4.5.1. • Clarification on the timing of the LNSC ad UFC sample collections relative to dosing with dexamethasone to account for the half-life of dexamethasone. The following sections are impacted by this change: Section 6.4.5.3 and Appendix A (Table 7). • Clarification on the scope of the interim analysis that will be performed and who will remain blinded at the individual subject level until the database lock at the end of the study. The following sections are impacted by these changes: Section 8.3.3.1 and Section 12.6. • Clarification that the analyses for the SONICS-completer Population will be performed only if the size of this cohort is at least 30% of the ITT population. This change impacts the Synopsis (Analysis Populations) and Section 12.1.	

• Clarification that the calculation of study drug compliance will be performed by phase and for the study overall instead of by visit. This change impacts Section 12.5.2.1. • Clarification on the categories to apply to the results from the oral glucose tolerance testing. This change impacts Section 12.5.2.6. • Clarification on the use of the two-sample t-test to compare the two randomized treatment groups. The two-sample t-test will be performed on the changes from Baseline (RW0) at each applicable visit in the Randomized Phase only and will not be performed for visits at the Restoration Phase. This change impacts Synopsis (Statistical methods) and Section 12.5.3.2. • Clarification on the analysis time points for the Cushing's Syndrome Quality of Life Questionnaire and Beck's Depression Questionnaire. The changes from Baseline (RW0) will be analyzed at the end of the Randomized Withdrawal Phase and Restoration Phase. This change impacts Section 12.5.3.2. • Clarification on Pregnancy test (βhCG) to include all women regardless of childbearing potential. This change impacts Appendix B (Other analytes/measures).	

SPONSOR APPROVAL

A Double-blind, Placebo-Controlled, Randomized Withdrawal Following Open-label Therapy Study to Assess the Safety and Efficacy of Levoketoconazole (2S, 4R-ketoconazole) in the Treatment of Endogenous Cushing's Syndrome

Signature: _____ Date: 23 Sep 2019

Fredric Cohen, MD
Chief Medical Officer

INVESTIGATOR AGREEMENT

I have read this protocol and agree:

- To conduct the study as outlined herein, in accordance with current International Council for Harmonisation (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: A Double-blind, Placebo-Controlled, Randomized Withdrawal Following Open-label Therapy Study to Assess the Safety and Efficacy of Levoketoconazole (2S,4R-ketoconazole) in the Treatment of Endogenous Cushing's Syndrome

Study center(s): This is a multicenter study at approximately 40 sites in North America, Europe and the Middle East. Additional sites may be added.

Phase of development: Phase 3

Objectives:

Primary: To determine the effect of withdrawing to placebo versus continuing treatment with levoketoconazole on the cortisol therapeutic response previously established during open-label levoketoconazole therapy.

Secondary:

1. To compare the effects of levoketoconazole with placebo on cortisol status (inferred from mean urinary free cortisol [mUFC] and/or late night salivary cortisol [LNSC]) during the Randomized Withdrawal (RW) Phase and the subsequent Restoration Phase;
2. To compare the effects of levoketoconazole with placebo on changes in biomarkers of CS comorbidities (fasting glucose, fasting insulin, homeostatic model assessment-insulin resistance [HOMA-IR], hemoglobin A1c [HbA1c], total cholesterol, low-density lipoprotein-cholesterol [LDL-C], and high-sensitivity C-reactive protein [hsCRP]);
3. To compare the effects of levoketoconazole with placebo on changes in health-related quality of life (QoL) and symptoms of depression;
4. To compare the effects of levoketoconazole with placebo on changes in acne, hirsutism and peripheral edema;
5. To assess the safety and tolerability of levoketoconazole;
6. To evaluate the population pharmacokinetics (PK) of levoketoconazole in subjects with CS.

NOTE: Secondary Objectives 5 and 6 are not subjects of hypothesis tests.

Exploratory:

1. To assess changes in anti-diabetic, anti-cholesterol, anti-hypertensive, and chronic anti-inflammatory therapies;
2. To describe the effects and durations of levoketoconazole action with respect to cortisol status and clinical signs and symptoms of CS other than acne, hirsutism and peripheral edema;
3. To describe the dose-response relationship of levoketoconazole with respect to safety and tolerability;
4. To describe the effects of levoketoconazole on glucose tolerance among subjects with impaired fasting glucose (IFG).

Criteria for evaluation:

Primary endpoint:

Proportion of subjects with loss of therapeutic response to levoketoconazole upon withdrawing to placebo compared with the proportion of subjects with loss of therapeutic response upon continuing treatment with levoketoconazole. Loss of therapeutic response (i.e. relapse) is inferred based on mUFC from three 24-hour urinary free cortisol (UFC) measurements obtained at any visit from second through final Randomized Withdrawal Phase visits (RW1 through RW5 inclusive) when:
(1) mUFC is above 1.5X the ULN of the central laboratory's reference range, OR
(2) mUFC is more than 40% above the baseline (RW0) value, if the RW0 value is above the ULN (i.e. >1.0X ULN)[1], OR
(3) an early rescue criterion is met.

Secondary endpoints:

- Changes from Baseline (RW0) in mUFC and LNSC at all post-Baseline visits with these assessments through the final study visit (RES2)—applies to Secondary Objective 1;
- Proportion of subjects with normalization of mUFC at RES2—applies to Secondary Objective 1;
- Proportion of subjects with normalization of mUFC at the end of Randomized Withdrawal Phase—applies to Secondary Objective 1;
- Changes from Baseline (RW0) in biomarkers of CS comorbidities (fasting glucose, fasting insulin, homeostatic model assessment-insulin resistance [HOMA-IR], hemoglobin A1c [HbA1c], total cholesterol, low density lipoprotein-cholesterol [LDL-C], and high-sensitivity C-reactive protein [hsCRP]) at all post-Baseline visits with these measurements through the final study visit (RES2)—applies to Secondary Objective 2;
- Changes from Baseline (RW0) in health-related QoL and symptoms of depression at all post-Baseline visits with these assessments through the final study visit (RES2) – applies to Secondary Objective 3;
- Changes from Baseline (RW0) in acne, hirsutism and peripheral edema at all post-Baseline visits with these assessments through the final study visit (RES2) – applies to Secondary Objective 4;
- Incidence and severity of adverse events (AEs), particularly adverse events of special interest (AESIs) during levoketoconazole open-label therapy in the Dose-Titration and Maintenance (TM) Phase (levoketoconazole-naïve cohort), and during blinded therapy in the Randomized Withdrawal Phase and Restoration Phase (both cohorts)—applies to Secondary Objective 5.

Pharmacokinetic endpoints and pharmacokinetic/pharmacodynamic modeling:

- Estimates of the following PK parameters: clearance (CL/F), volume of distribution (V/F), absorption rate constant (Ka), with associated between-subject variability where feasible. These parameters will be used to calculate half-life (t½), area under the concentration time curve (AUC) and peak concentration (Cmax), if feasible—applies to Secondary Objective 6;
- Estimates of the following pharmacodynamic (PD) parameters: levoketoconazole concentration producing half maximal UFC suppression (IC 50), maximal suppression of UFC (Imax) and associated estimates of between-subject variability, if feasible. UFC concentrations in relation to dose and plasma exposure will be explored—applies to Secondary Objective 6.

Exploratory endpoints:

- Frequency of usage and changes from Baseline (RW0) in frequency of usage of anti-diabetic, anti-cholesterol, anti-hypertensive, and chronic anti-inflammatory therapies at all post-Baseline visits; changes in corresponding biomarkers accounting for changes in medication usage will also be explored—applies to Exploratory Objective 1;

- Time from RW0 to first time of loss of response, when:
  (1) mUFC is above 1.5X the ULN of the central laboratory's reference range, OR
  (2) mUFC is more than 40% above the RW0 value, if the RW0 value is above the ULN [i.e. >1.0X ULN][2], OR
  (3) an early rescue criterion is met—applies to Exploratory Objective 2;
- Time to first normalization of mUFC beginning from RW5 (subset with mUFC above 1.5X ULN at RW5)—applies to Exploratory Objective 2;
- Time to first normalization of LNSC beginning from RW5 (subset with LNSC above ULN at RW5)—applies to Exploratory Objective 2;
- Proportion of subjects with normalization of mUFC at the end of Dose Titration and Maintenance Phase (TM7)—applies to Exploratory Objective 2;
- Proportion of subjects with either normalization of mUFC or partial response (at least 50% decrease in mUFC) at the end of Dose Titration and Maintenance Phase (TM7)—applies to Exploratory Objective 2;
- Proportion of subjects with normalization of LNSC at RES2—applies to Exploratory Objective 2;
- Changes from Baseline (RW0) in serum cortisol and adrenocorticotrophic hormone (ACTH) at all post-Baseline visits with these assessments through the final study visit (RES2)—applies to Exploratory Objective 2;
- Changes from Baseline (RW0) in clinical signs and symptoms of CS excluding acne, hirsutism and peripheral edema at all post-Baseline visits with these assessments through the final study visit (RES2)—applies to Exploratory Objective 2;
- Frequency and severity of common AEs and laboratory abnormalities in relation to dose of study drug administered at the time of the reported AE or laboratory abnormality—applies to Exploratory Objective 3;
- Shifts from normality and concentration changes from Baseline (RW0) in serum transaminases, alkaline phosphatase, and total bilirubin at all post-Baseline visits in relation to dose of study drug administered at the time of the shift or change—applies to Exploratory Objective 3;
- Durations and changes in durations from Baseline (RW0) of the QT interval corrected for heart rate (QTc) in relation to dose of study drug administered proximal to the measurement—applies to Exploratory Objective 3.
- Change from Baseline in observed and derived glucose and insulin parameters during oral glucose tolerance test (OGTT) in the subset of subjects with IFG—applies to Exploratory Objective 4.

Methodology: A study schematic follows at the end of this section. This is a double-blind, randomized, placebo-controlled withdrawal and restoration (or as needed early rescue) study in subjects with endogenous CS previously treated with single-arm, open-label levoketoconazole that will assess efficacy, safety, tolerability, and PK of levoketoconazole. Two populations or cohorts, are defined for analytical and procedural purposes as follows:
Levoketoconazole-naïve cohort: Subjects who did not participate in the prior clinical study of

[1] This category applies only to subjects who have completed SONICS, who may have a Therapeutic Dose established with UFC above the ULN of the reference range. Levoketoconazole-naïve subjects must have UFC at or below the ULN at RW0 to qualify for randomization.

[2] This category applies only to subjects who have completed SONICS, who may have a Therapeutic Dose established with UFC above the ULN of the reference range. Levoketoconazole-naïve subjects must have UFC at or below the ULN at RW0 to qualify for randomization.

Open-label levoketoconazole	Therapeutic Dose established from Dose Titration and Maintenance (TM) Phase for levoketoconazole-naïve cohort, or prior to entry into LOGICS for the SONICS-completer cohort	
Randomization (RW0)	⇩	⇩
Blinded Randomized Withdrawal Phase	**Levoketoconazole** at Therapeutic Dose	**Placebo** at equivalent tablet count to Therapeutic Dose
Blinded Restoration Phase	**Placebo** added as 1 tablet twice daily (BID) at RW5 then add 1 tablet every 2 days, alternating AM and PM, until the total tablet count is double the count at RW0	**Levoketoconazole** added as 1 tablet BID at RW5 then add 1 tablet every 2 days, alternating AM and PM, until the total tablet count is double the count at RW0

levoketoconazole (COR-2012-01 aka SONICS) **plus** subjects who completed Visit M12 of SONICS (final scheduled visit prior to safety follow-up) but who have not been treated with a Therapeutic Dose of levoketoconazole throughout the 12-week period immediately prior to Screening in the current study.
SONICS-completer cohort: Limited to subjects who have completed all visits in the SONICS study through M12 (final scheduled visit prior to safety follow-up) at any time prior to the current study **and** who have been treated with a stable Therapeutic Dose of levoketoconazole throughout the 12-week period immediately prior to Screening.

Study methodology varies by cohort prior to randomization (RW0) only. Following initial Screening (washout as needed) and Dose Titration and Maintenance (TM) Phase, as applicable, this study will be conducted in two randomized, double-blind treatment phases (a Randomized Withdrawal Phase and a Restoration Phase).

Screening Phase:

Duration up to approximately 13 weeks to allow for washout, as needed.

All subjects on levoketoconazole from SONICS or the Expanded Access Program (EAP) must have confirmation of their Therapeutic Dose, as defined in the SONICS protocol, during the Screening Phase to confirm cohort placement for LOGICS. During this time, subjects will continue their prescribed dose of levoketoconazole to ensure continuity of treatment.

Subjects who have completed all visits in SONICS, through Visit 12 and have been on a stable Therapeutic Dose throughout the 12-week period immediately prior to signing informed consent, will enter the Screening Phase to confirm eligibility.

For subjects who have completed SONICS within 6 months prior to Screening for LOGICS, the Screening Phase, relying primarily on data collected during SONICS and completed with data collected in LOGICS, will begin after Visit M12 of SONICS completion and end once eligibility is confirmed. The time from confirmation of eligibility to RW0 should be no more than 11 (+3) days later (the minimum time requirement for Therapeutic Dose confirmation as dictated by tolerability and UFC results). As data collected from the SONICS study will be used in this study as well, overlapping assessments only need to be performed once (e.g. the same vital signs data may be recorded in the eCRFs for both studies).

For subjects who have completed SONICS more than 6 months prior to the Screening Phase and have been on a stable Therapeutic Dose throughout the previous 12-week period, Screening procedures will mimic those for the levoketoconazole-naïve subjects to confirm eligibility for the current study. After eligibility has been confirmed during the Screening Phase, subjects should proceed directly to the

Baseline/Randomization Visit (RW0). The time between Screening and RW0 should be no more than 11±3 days.

Following consent signature, subjects naïve to levoketoconazole receiving previous CS medical therapies or other prohibited medications must enter a washout period before completing screening assessments detailed in the Time and Events schedule. The Screening Phase may last up to approximately 13 weeks. Baseline measurements will be obtained as part of the Screening assessments (after washout); therefore, the time from confirmation of eligibility to TM0 (aka Baseline) should be no more than 11 (+3) days. Screening procedures completed within 3 weeks of TM0 (within 2 weeks for LNSC, QTc interval and liver safety tests) will be used as the TM0 value. If Screening procedures were completed more than 3 weeks prior to TM0, then they will be repeated at TM0 (except for pituitary magnetic resonance imaging (MRI), which may be completed up to 6 months of TM0 or RW0). All blood samples (except for post dose PK samples) should be obtained prior to administering the first dose of levoketoconazole.

Likewise, the final Baseline UFC specimen should be collected close to the date of TM0 and never more than 6 weeks prior to TM0. NOTE: all Baseline UFC and LNSC values must be obtained after washout of any medications that are known to influence cortisol levels.

If a subject does not meet the eligibility requirements on initial Screening, they may be eligible to re-screen only if worsening of their medical condition has increased the likelihood that they would meet the study eligibility criteria. Such re-screenings will be exceptional circumstances, and all re-screenings require prior permission of the study Medical Monitor before they begin. Repeating a Screening test (e.g. UFC) that has been found to be technically flawed will not be considered re-screening.

For subjects who have completed Visit M12 in SONICS either within the previous 6 months or more than 6 months prior to the Screening Phase and are NOT on a stable Therapeutic Dose throughout the previous 12-week period, Screening procedures will mimic those for the levoketoconazole-naïve subjects as noted above to confirm eligibility and progress the subject into the Dose Titration and Maintenance (TM) Phase of the study.

Dose Titration and Maintenance (TM) Phase (**levoketoconazole-naïve cohort ONLY**)

After confirmation of eligibility, members of the levoketoconazole-naïve cohort (including subjects that completed SONICS but require re-titration) will enter the TM Phase. As detailed above, subjects who completed visit M12 of SONICS but who have not been treated with a stable Therapeutic Dose of levoketoconazole throughout the 12-week period immediately prior to screening must establish their Therapeutic Dose in the TM Phase and are thus members of the levoketoconazole-naïve cohort. The starting dose for these subjects may be as high as the dose that was most recently or currently being received or next higher dose level, at the discretion of the Investigator. The first dose of open-label therapy for this phase will be at TM0. Dose titration will occur in increments of 150 mg over a period of approximately 3 to 19 weeks to achieve an effective and tolerable dose (the Therapeutic Dose). In exceptional situations, subjects may require additional time (i.e. greater than 19 weeks) to achieve the Therapeutic Dose. These situations must be approved on a case by case basis by the Medical Monitor. Dose increases (and decreases, as needed) will be based on subjective and objective indicators of medication tolerance, UFC and other cortisol measures. Subjects will return to the clinic every 14 (± 3) days during the TM Phase (note: to allow for 4 weeks maintenance, additional time may be required in the event a dose change is required at TM7). Additionally, when a dose escalation during the TM Phase is required to a total daily dose of 750 mg or above, subjects will be asked to return to the clinic or, optionally, will be visited by a qualified home healthcare (HHC) professional for one extra safety evaluation 5 days (± 2 days) after each dose escalation.

Subjects will be advised to contact the Investigator immediately in the event of AESI-suggestive signs or symptoms (defined later) regardless of the onset timing relative to a scheduled visit.

Once the Therapeutic Dose has been reached and confirmed from the mean of a total of three adequately collected 24-hour urine specimens for UFC measurements, subjects will continue that Therapeutic Dose (i.e. in Maintenance) until the final open-label study visit (Visit TM7) in the TM Phase. During the TM Phase (while treatment is open-label), once the Therapeutic Dose is achieved, the dose should generally not be further adjusted if the UFC levels are within normal limits. However, the dose may be increased if medically necessary to maintain eucortisolemia or decreased to address drug intolerance or AE. Prior to the final open-label visit (Visit TM7), three complete 24-hour urine specimens will be obtained (collections need not be repeated if the final open-label visit coincides with the initial establishment of UFC normalization) to confirm maintenance of UFC normalization prior to randomization, denoting UFC-eligibility for the Randomized Withdrawal Phase. To ensure the TM Phase occurs within the allotted timeframe of no more than approximately 19 weeks, urine collections should ideally be made on sequential days and prior to the actual scheduled visit for dose assessment, as results are needed to determine if dose escalation is required, or whether a confirmatory UFC is needed to establish Therapeutic Dose. The minimum duration of this phase and thus establishment of the Therapeutic Dose will be no less than approximately 14 weeks, even among subjects who reach a Therapeutic Dose more quickly. Randomization (RW0) should occur as soon as possible after the final Titration-Maintenance visit (TM7) and no more than 11 (+3) days later unless a dose change was required at Visit TM7. Regardless, in all cases at least 4 weeks should elapse between reaching the Therapeutic Dose and RW0 to ensure tolerability and stability (continued effectiveness) of the Therapeutic Dose.

Subjects still in the TM Phase when the randomization target of 46 to 54 subjects, depending on the observed withdrawal rate trend during the Randomized Withdrawal Phase is reached, will be offered the opportunity to join an open-label extension (OLE) study (Study COR-2017-OLE, aka OPTICS) to receive open-label treatment. Subjects must meet the OPTICS inclusion/exclusion criteria to be eligible.

<u>Randomized Withdrawal (RW) Phase (All Subjects)</u>

In the 8-week, double-blind Randomized Withdrawal Phase, subjects will return to the clinical site at least twice: on RW3 {Day 30(-4)} and RW5 {Day 58(-4)} relative to the Randomization Visit (RW0) for safety and efficacy evaluations to determine if they are still responding to therapy, or if they have relapsed or if an early rescue criterion has otherwise been met.

Three additional visits, either at-home (by a qualified HHC professional) OR on-site, will be conducted for all subjects on RW1 {Day 10(-2)}, RW2 {Day 20(-2)} and RW4 {Day 40(-2)} relative to Randomization (RW0). These interim visits will be primarily for determining cortisol status as well as to monitor safety and tolerability associated with the possible withdrawal of medication. Partial loss of response or relapse should be confirmed by a repeat 24-hour urine sample or LNSC sample, which should be collected and analyzed as soon as possible. Courier services will be provided, as desired, to collect UFC specimens for transport to the site on days when a qualified HHC professional is not present or if subjects prefer courier pickup of collected samples prior to visit.

NOTE: Early rescue criteria are described that provide for **immediate** substitution of blinded study drug with open-label levoketoconazole treatment directed by the study Investigator if continued use of blinded treatment is regarded as unacceptable owing to significant or rapid clinical deterioration. Criteria to guide the Investigator as to the possible need for early rescue medication are described in this protocol. Although UFC will be the primary measure of loss of therapeutic efficacy, cortisol status will be assessed through additional measures as described. The rapid titration schedule used in the Restoration Phase should be used to reestablish the Therapeutic Dose if a subject requires early rescue with open-label levoketoconazole. As treatment is open-label during early rescue, dose adjustments may be made, as medically indicated. This includes adjustments to dose levels above the previous therapeutic dose if required to return subject to eucortisolemia.

<u>Restoration Phase (All Subjects)</u>

All subjects completing the 8-week Randomized Withdrawal Phase who do not meet early rescue criteria, will enter the Double-blind Restoration Phase, wherein they will continue to receive the randomly assigned blinded treatment regimen and in addition will receive blinded restoration study medication (placebo for those already receiving levoketoconazole; levoketoconazole for those already receiving placebo), beginning with 1 tablet BID and titrated in 1 tablet increments every 2 days alternating AM and PM, as described above, in order to return their treatment regimen to its status quo prior to randomization (i.e. subjects will resume the Therapeutic Dose of levoketoconazole if randomized to placebo in the Randomized Withdrawal Phase). The total tablet number received during blinded Restoration Phase will ultimately be twice the number received prior to randomization. If, in the opinion of the Investigator, an increased dose of study drug is required for subjects who are unable to restore their prior cortisol control (i.e. mUFC >ULN) during the Restoration Phase at their prior Therapeutic Dose, those subjects should be withdrawn from this study owing to "loss of efficacy". Such subjects may be considered for enrollment in the long-term OPTICS study or EAP if they otherwise qualify.

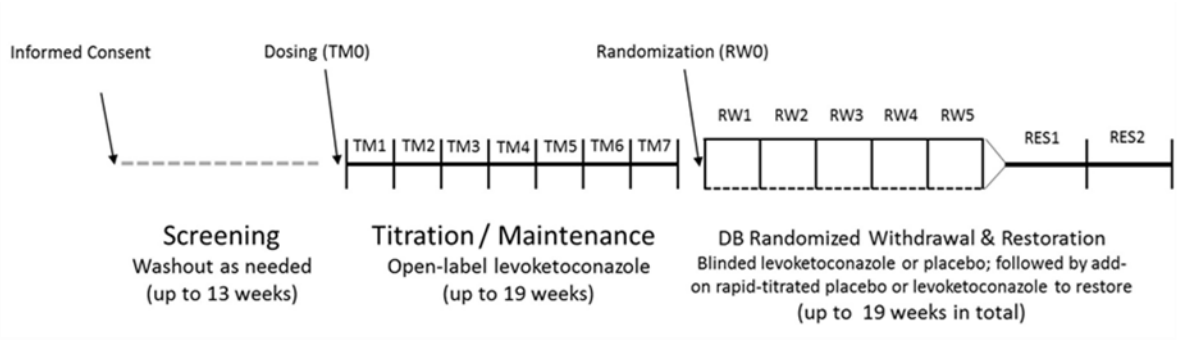
Safety monitoring and extended assessment

Throughout the study, safety data will be collected at regular intervals of approximately: 5 to 17 days during Titration and Maintenance, 6 to 20 days during Randomized Withdrawal and 23 to 33 days during Restoration Phase (except for interim, remote [via telephone], safety checks during rapid titration), per the Time and Events Schedule. Adequate medical coverage must be provided by the study site continuously during the study to ensure that prompt safety decisions can be made and appropriate medical interventions provided. The Investigator will provide subjects with instructions for accessing medical staff at any hour to obtain prompt medical care. An independent Data Safety Monitoring Board (DSMB) will review key safety data at regular intervals throughout the study, including review of serious adverse events (SAEs) and AESIs shortly after they have been reported to the Sponsor.

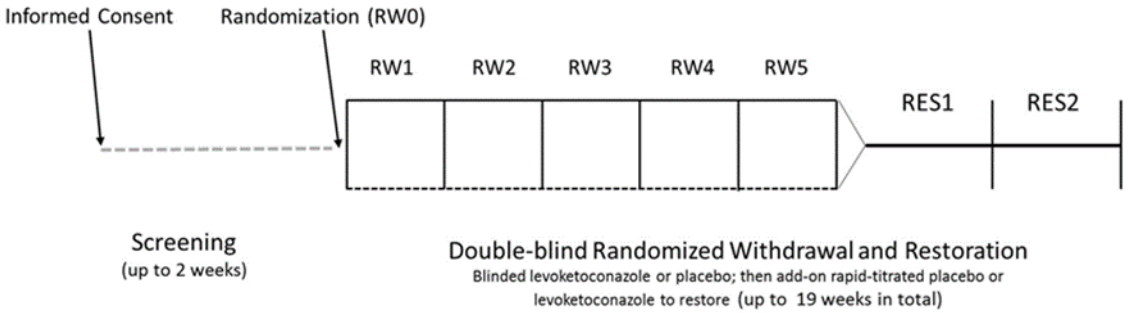
Study completion is defined as having: completed all scheduled visits in the Restoration Phase **OR** required early rescue with open-label levoketoconazole (or another rescue medication) during the Randomized Withdrawal Phase. If early rescue is deemed appropriate with open-label levoketoconazole, subjects continue in the study using Blinded Restoration Phase procedures. Subjects requiring rescue medication should complete all procedures for visit RW5 prior to entering the Restoration Phase. All subjects who complete the study will be eligible to enter the open-label extension (OLE) OPTICS study to continue open-label treatment with levoketoconazole and enable assessment of the long-term effects on efficacy and safety. The OPTICS study is described in a separate protocol.

Levoketoconazole-naïve cohort

[Levoketoconazole-naïve subjects (or re-titrations)]



SONICS-completer cohort



Note: RW5, the last visit of the Randomized Withdrawal, marks the start of the Restoration Phase

NOTE: If there is a time gap between completion of Screening and TM0 or RW0 for subjects currently receiving levoketoconazole, then open-label levoketoconazole should be continued between Screening and TM0 or RW0 to maintain the Therapeutic Dose. If rolling over from SONICS, subjects will be dispensed LOGICS medication starting at the screening visit. If entering from the expanded access program (EAP), subjects will stay on open-label levoketoconazole dispensed from EAP until the Baseline visit.

Number of subjects (planned): Forty-six (46) to 54 subjects, 23 to 27 in each treatment group, will be enrolled into the Randomized Withdrawal Phase of the study. A minority of randomized subjects are anticipated to be subjects in the SONICS-completer cohort. Any subject who withdraws after randomization will not be replaced. Withdrawn subjects will not be re-entered into the study.

Study Hypothesis and Sample Size Determination: The null hypothesis is that the proportion of subjects with loss of therapeutic response, upon withdrawing to placebo compared with continued levoketoconazole, is not different between levoketoconazole and placebo. The alternative hypothesis is that the two proportions are different, specifically that there is an increased loss of response for the placebo arm. For the purpose of sample size estimation, it is assumed that among subjects in the ITT population who complete at least the RW4 visit in the Randomized Withdrawal Phase, 10% will lose therapeutic response in the levoketoconazole arm vs. 75% in the placebo arm. For the analysis of the primary endpoint, subjects in the ITT population who withdraw prior to RW4 will be considered as losing therapeutic response.

A minimum of 46 subjects (23 per arm) and a maximum of 54 subjects (27 per arm) will be targeted to be enrolled into the Randomized Withdrawal Phase based on the observed withdrawal rate trend for the

phase. If the withdrawal rate is 10% per arm, a sample size of 46 subjects (23 per arm) randomized and treated during the Randomized Withdrawal Phase corresponds to 42 subjects (21 per arm) completing RW4 and provides approximately 99% power to detect the alternative hypothesis of a loss of therapeutic response rate of 17% in the levoketoconazole arm and 78% in the placebo arm vs. the null hypothesis. If the withdrawal rate is 20% per arm, a sample size of 54 subjects (27 per arm) randomized and treated during the Randomized Withdrawal Phase corresponds to 44 subjects (22 per arm) completing RW4 and provides approximately 98% power to detect the alternative hypothesis of a loss of therapeutic response rate of 26% in the levoketoconazole arm and 81% in the placebo arm vs. the null hypothesis.

Eligibility for Enrollment

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

Inclusion Criteria for Specified Subjects Completing the SONICS Study:

Subjects who have completed the SONICS study, within 6 months of the screening visit, including those receiving open-label treatment after SONICS as part of an EAP, may be eligible for the study if the following criteria are met:

1. Completed the final SONICS visit (M12) and have demonstrated maintenance of clinical response (partial or complete, as defined in the SONICS protocol, COR-2012-01) on a stable Therapeutic Dose of levoketoconazole for at least 12 weeks prior to study entry (i.e. Visit RW0).
2. Able and willing 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.

Inclusion Criteria for All Others:

The following categories of potential subjects, categorized by prior use of levoketoconazole, may be eligible if the following 11 inclusion criteria are all met:

- Naïve to levoketoconazole (defined as having never participated in SONICS);
- Completers of SONICS visit M12 more than 6 months of the screening visit of the current study;
- Completers of SONICS visit M12 within 6 months of the screening visit who have not been receiving a stable Therapeutic Dose of levoketoconazole for at least 12 weeks prior to the start of screening.

1. Male or female and at least 18 years of age.
2. Able and willing 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.
3. Confirmed newly diagnosed, persistent or recurrent endogenous Cushing's syndrome of any etiology, except secondary to malignancy (including pituitary or adrenal carcinoma). Persistence will not be considered confirmed until 6 weeks or more post-surgery.
   The following historical evidence will be considered as sufficient to establish the cause of endogenous Cushing's syndrome as being due to Cushing's disease (i.e. ACTH-dependent of pituitary origin) specifically:
   - Pathological (e.g. adrenocorticotropic hormone [ACTH]-staining) or post-surgical confirmation of the diagnosis of CD (i.e. documented adrenal insufficiency post-adenomectomy or post-hypophysectomy) **OR**
   - Intermediate, normal or elevated plasma ACTH (i.e. at least 5 pg/mL [1.1 pmol/L]) **PLUS**
     <u>For tumors 6 mm and above by imaging:</u>
     a) Inferior petrosal sinus sampled (IPSS) ACTH central:plasma gradient at least 2 before corticotropin-releasing hormone (CRH) or at least 3 after CRH, OR in the absence of IPSS, either:

b) Positive ACTH and/or cortisol response to CRH or desmopressin or combined CRH-desmopressin stimulation plus high-dose (8 mg) dexamethasone suppression of blood cortisol, ideally on more than one occasion OR

c) Other adequate diagnostic testing. Such cases must be discussed with and explicitly approved by the Medical Monitor, and the specific diagnostic criteria used to establish the diagnosis of CD must be documented.

For tumors below 6 mm or not visible by Magnetic Resonance Imaging (MRI):

a) IPSS with ACTH central:plasma gradient at least 2 before CRH or at least 3 after CRH.
b) Other adequate diagnostic testing. In the absence of IPSS, an individual might be eligible if CD was otherwise confirmed via adequate testing. Such cases must be discussed with and explicitly approved by the Medical Monitor, and the specific diagnostic criteria used to establish the diagnosis of CD must be documented.

4. Elevated mean 24-hour UFC levels at least 1.5X ULN of the normative range of the study's central laboratory assay and from a minimum of three measurements from adequately collected urine; the study's central laboratory must be used for all qualifying measurements.

   NOTE: This criterion does not apply to subjects currently on levoketoconazole.

5. Presence of abnormal values from at least one of these two diagnostic tests (discrepancies between test findings will not be investigated nor considered exclusionary)

   - Abnormal Dexamethasone Suppression Test (DST): Elevated 8 AM blood cortisol at least 1.8 µg/dL (50 nmol/L) after 1 mg dexamethasone orally at 11 PM the evening prior with concurrent dexamethasone blood concentration greater than 5.6 nmol/L (220 ng/dL) (results from within the 2 months prior to start of Screening or newly tested with results available by the Baseline Visit [TM0]). If the DST cortisol is elevated and the dexamethasone value is at least 3.9 nmol/L (153 ng/dL), then the subject could qualify if at least 1 LNSC is greater than the ULN of the study's central laboratory normative range (the study's test kit and lab must be used for all qualifying measurements), whereas a non-suppressed cortisol during DST with a dexamethasone value of at least 5.6 nmol/L (220 ng/dL) would be required if LNSC is not done or if both LNSC values are low (≤ ULN of the study's central laboratory normative range; the study's test kit and lab must be used for all qualifying measurements).

   OR

   - Elevated LNSC concentrations (at least two measurements) each greater than the ULN of the study's central laboratory normative range; the study's test kit and lab must be used for all qualifying measurements.

   NOTE: Abnormal LNSC is required among eligible subjects with estimated glomerular filtration rate (eGFR as determined by Modified Diet in Renal Disease MDRD equation) above 40 and below 60 mL/min/1.73 m^2.

   NOTE: This criterion does not apply to subjects currently on levoketoconazole.

6. Non-candidates for CS-specific surgery, refuse surgery or surgery will be delayed until after study completion and agree to complete this study prior to surgery.
7. If post-surgical for CS-specific surgery, then no significant post-operative sequelae remain and the risk of such sequelae is considered negligible.
8. Agree to the following minimum washout periods prior to the Baseline Visit (TM0) (as applicable):

   - 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.

9. Females who are either of non-child bearing potential (i.e. incapable of becoming pregnant):
   - Post-menopausal, defined as age 50 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) OR
   - Surgically sterile—documented hysterectomy and/or bilateral oophorectomy or tubal ligation

   OR
   - Females of child-bearing potential who agree to use highly effective methods of birth control while participating and for 2 weeks after participation has completed (abstinence is considered acceptable if routinely practiced).
10. Men who, if fertile, agree to use an acceptable form of birth control, including abstinence if routinely practiced, while enrolled and for 2 weeks after participation has completed.
11. Able to comprehend and comply with all procedures.

Exclusion Criteria

Subjects will be excluded from the study if ANY of the following criteria are met (NOTE: exclusion criteria apply to and must be assessed in both cohorts):

1. Enrolled in SONICS but have not completed SONICS through Visit M12.
2. Pseudo-Cushing's syndrome based on assessment of the Investigator.
3. Cyclic Cushing's syndrome with multi-week periods of apparent spontaneous CS remission.
4. Non-endogenous source of hypercortisolism, including pharmacological corticosteroids or ACTH.
5. Radiotherapy of any modality directed against the source of hypercortisolism within the last 5 years.
6. Treatment with mitotane within 6 months of 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. Clinical or radiological signs of compression of the optic chiasm.
9. Major surgery within 1 month of Screening (or within 6 weeks for pituitary surgery).
10. Clinically significant abnormality in 12-lead electrocardiogram (ECG) during the Screening Phase requiring medical intervention (may be eligible once stable, to be determined case by case).
11. QTc interval above 470 msec during the Screening Phase via central reader interpretation.
12. History of Torsades des Pointes, ventricular tachycardia, ventricular fibrillation, history of prolonged QT syndrome (including first-degree family history).
13. Use of medications associated with possible, probable, or definite QT/QTc prolongation (unless subsequently washed out).
14. Pre-existing hepatic disease (except for mild to moderate non-alcoholic fatty liver disease documented by imaging or biopsy and with transaminase values within allowed limits).
15. Hepatitis B surface antigen (HbsAg) or hepatitis C-positive.
16. Human immunodeficiency virus (HIV)-positive.
17. History of symptomatic cholelithiasis with intact gallbladder.
18. History of pancreatitis.
19. Liver safety tests during the Screening Phase as follows:

- Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) above 3X ULN
- Alkaline phosphatase or Total bilirubin above 2X ULN.
  Subjects with isolated indirect bilirubin up to 3X ULN are presumed to have Gilbert's syndrome and may be enrolled if all other liver safety tests are within normal levels.

20. History of documented or suspected drug-induced liver injury to ketoconazole or any other azole drug.
21. Serum potassium below 4.0 mEq/L (unless subsequently corrected and stable).
22. 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.
23. History of persistent, uncontrolled hypertension despite medical intervention.
24. Hypercholesterolemia currently treated with atorvastatin, lovastatin or simvastatin and unwilling or unable to change to alternative therapy with: pravastatin, fluvastatin, pitavastatin or rosuvastatin (must switch statin at least 2 weeks prior to dosing) or another allowed therapy. For subjects for whom lipid reduction therapy is being considered, all lipid lowering drugs should be added and stabilized for at least 4 weeks prior to TM0 for the levoketoconazole-naïve cohort or RW0 for the SONICS-completer cohort, as improvements in lipids are being assessed as an endpoint for levoketoconazole treatment in this study.
25. More than one hospitalization for hyperglycemia or complication of diabetes during the last 12 months
26. Decreased renal function as defined by eGFR below 40 mL/min/1.73 m^2, using MDRD equation for eGFR.
27. Pregnant or lactating.
28. Body habitus preventing repeated venipuncture as required by protocol.
29. Any other clinically significant medical condition, as determined by the Investigator that precludes enrollment and participation in the study through completion, including conditions that would preclude the subject from being able to follow instructions or perform necessary procedures (for example, psychiatric instability or severe disability).
30. History of alcohol or drug abuse in the 6-month period prior to Screening.
31. Currently participating in another study or has received any investigational treatment (drug, biological agent or device) other than levoketoconazole (COR-003), within prior 30 days or five half-lives of treatment, whichever is longer.
32. 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). A list of acceptable oral antacids will be provided; if used, antacids must be ingested at least 2 hours after dosing of levoketoconazole.
33. Current use of any prohibited concomitant medication that cannot be discontinued safely and washed out completely prior to the Baseline Visit (TM0 or RW0, for the levoketoconazole-naïve and SONICS-completer cohorts, respectively), including but not limited to the following (a more complete list is included in Appendix J):
    - 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 rice yeast, danshen, silybum marianum, Asian ginseng, schissandra sphenanther, shankhapushi, and Asian herb mixture (Xiao chai hu tang and Salboku-to);
    - Topical or inhaled corticosteroids;
    - Carbamazepine, fenofibrate, carbenoxolone;

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

Investigational product, dosage and mode of administration:

Levoketoconazole (2S,4R-ketoconazole); 150 mg immediate release tablets for oral administration.

For the levoketoconazole-naïve subjects, the total daily dose will be titrated in 150 mg increments from a starting dose of 300 mg (dosed as 150 mg BID) up to a maximal daily dose of 1200 mg (dosed as 600 mg BID) until a Therapeutic Dose is established. Subjects re-establishing their Therapeutic Dose via re-titration may begin titration at their current or most recently received dose at the discretion of the Investigator. The minimum daily dose is 150 mg once daily (QD) for subjects who cannot tolerate 150 mg BID. For all subjects in the levoketoconazole-naïve cohort, the Therapeutic Dose will be established by the end of the TM Phase.

For the SONICS-completer cohort, the stable Therapeutic Dose will have been established prior to enrollment in this study.

The Therapeutic Dose will be used as the target dose and dose-regimen during the Restoration Phase.

Duration of treatment:

Prior to treatment, subjects in the levoketoconazole-naïve cohort (including subjects who completed SONICS Visit M12 but who have not been treated with a stable Therapeutic Dose of levoketoconazole throughout the 12 weeks immediately prior to screening) will undergo Screening for up to approximately 13 weeks (to allow for prior medication washout and to complete screening procedures); there is no required minimum Screening interval. Dose titration is variable depending on clinical response. However, all subjects in the levoketoconazole-naïve cohort will be treated for not less than 14 weeks in total and for no more than approximately 19 weeks (except on a case by case basis with approval by the Medical Monitor) in total during the TM Phase to confirm the Therapeutic Dose and to establish tolerability to levoketoconazole. The Randomized Withdrawal Phase and the Restoration Phase are each approximately 8 weeks' duration (maximum 9½ weeks), with the total of the two treatment phases not to exceed approximately 19 weeks. Therefore, the longest anticipated exposure to active study medication in this study is no more than approximately 38 weeks and the shortest approximately 8 weeks. The longest anticipated exposure to placebo monotherapy is no more than 9½ weeks. The longest anticipated total study participation duration is approximately 51 weeks.

Reference therapy, dosage and mode of administration:

An active reference therapy will not be used. Placebo tablets identical in appearance to levoketoconazole will be administered during the Randomized Withdrawal Phase using the same regimen as the Therapeutic Dose of levoketoconazole established during the TM Phase (levoketoconazole-naïve cohort) or at study entry (SONICS-completer cohort). During the Restoration Phase, blinded placebo to be added onto the levoketoconazole regimen will be started at 1 tablet BID and titrated every 2 days in 1 tablet increments per the Dosing Titration Scheme until the Therapeutic Dose-equivalent is achieved unless the Therapeutic dose is DL0. The total final tablet count (active + placebo) during Restoration Phase will equal twice the total tablet count of the Therapeutic Dose, not to exceed 8 tablets BID.

Analysis Populations:

Intent-to-Treat Population (ITT): The ITT population will include all subjects who are randomized and receive at least one dose of blinded study medication during the Randomized Withdrawal Phase. The ITT population will be used for the primary analysis of efficacy and secondary analyses of efficacy and safety.

Per Protocol (PP) Population: The PP population will consist of all subjects in the ITT population who have no major protocol deviations during the Randomized Withdrawal Phase that could affect the primary endpoint. This population will be used in supportive analyses of the primary endpoint and secondary efficacy endpoints.

Levoketoconazole-naïve Population: The levoketoconazole- naïve population will consist of all subjects in the levoketoconazole-naïve cohort who receive at least one dose of study medication during the TM Phase. This population will be used for supportive evaluations of safety and for exploratory efficacy, safety, and PK analyses.

SONICS-completer Population: The SONICS-completer population will consist of all subjects in the SONICS-completer cohort who receive at least one dose of blinded study medication during the Randomized Withdraw Phase. This population will be used for supportive evaluations of safety and for exploratory efficacy, safety, and PK analyses. Because only a minority of the subjects are anticipated to be in the SONICS-completer cohort, the analyses will be performed only if the size of this cohort is at least 30% of the ITT population.

Statistical methods:

Primary Efficacy Analysis: The primary analysis will use the ITT population and supportive analysis will be repeated in the PP population.

Statistical significance testing will be conducted using a logistic regression model containing fixed effect terms for Randomized Withdrawal treatment group (levoketoconazole, placebo) and subject cohort (SONICS-completer cohort, levoketoconazole-naïve cohort) and confirmed using a two-sided Fisher's Exact test.

Secondary Efficacy Analysis: Inferences derived from secondary efficacy analyses will be gated on results from the primary efficacy analysis. Secondary efficacy analyses will be hierarchically structured to ensure control of the family-wise type I error rate at the 0.05 level. Hypothesis tests for secondary endpoints will be based on null hypotheses that assume no *a priori* differences between placebo and levoketoconazole treatments. All secondary endpoints will be analyzed using the ITT population (primary analyses) and the PP population (supportive analyses).

Changes from Baseline (RW0) in mUFC and LNSC during the Randomized Withdrawal Phase will be analyzed using repeated measures mixed effects models with fixed effect terms for treatment group, subject cohort, time (i.e. visit) and treatment-by-time interaction, with Baseline value as a covariate and subject as a random effect. The treatment groups will be compared using least squares mean differences between treatment groups and associated 95% confidence intervals (CIs) for each time point will be derived from the model. Two-sample t-tests will also be performed to compare the two treatment groups for the mean change from Baseline to each nominal visit during the Randomized Withdrawal Phase.

Normalization of mUFC at RES2 will be calculated for each treatment group and presented as shift tables from RW5 to RES2 using three strata of mUFC status: at or below ULN, more than ULN and no more than 1.5X ULN, above 1.5X ULN.

The number and proportion of subjects with normalization of mUFC (at or below ULN) at the end of the Randomized Withdrawal Phase (RW5) will be summarized for each treatment group and compared using Fisher's Exact test (with corresponding 95% CIs).

Changes and percentage changes from Baseline (RW0) in the biomarkers of CS comorbidities (fasting glucose, fasting insulin, HOMA-IR, Hb1Ac, total cholesterol, LDL-C, and hsCRP) during the Randomized Withdrawal Phase and Restoration Phase will be summarized by treatment group and time point and assessed using two-sample t-test comparison at each visit in the Randomized Withdrawal Phase. For CS comorbidities measured at more than one visit after RW0 during the Randomized Withdrawal Phase, changes from Baseline during the Randomized Withdraw Phase will also be analyzed using repeated measures mixed effects models.

Changes from Baseline (RW0) in health-related QoL, symptoms of depression, acne, hirsutism and peripheral edema during the Randomized Withdrawal Phase and Restoration Phase will be summarized by treatment group and time point and mean changes from Baseline assessed using two-sample t-test comparison at the end of the Randomized Withdrawal Phase.

Safety Analyses: Safety assessments, including AEs, vital signs, ECGs (inclusive of QTc), laboratory parameters, and physical examination results will be summarized descriptively by study phase and/or by time point, as applicable.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACTH	Adrenocorticotropic hormone
ADA	American Diabetes Association
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
ANA	Antinuclear antibody
AP	Alkaline Phosphatase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
βhCG	Beta human chorionic gonadotropin
BDI-II	Beck Depression Inventory
BID	Twice daily
BMI	Body mass index
CBG	Cortisol-binding globulin
CFR	Code of Federal Regulations
CD	Cushing's disease
CI	Confidence Interval
CL/F	Apparent clearance following oral administration
Cmax	Peak concentration
CRF	Case Report Form
CRH	Corticotropin-releasing hormone
CRO	Clinical Research Organization
CRP	C-reactive protein
CS	Cushing´s syndrome
CYP	Cytochrome P450
GCP	Good Clinical Practice
DBP	Diastolic blood pressure
DCCT	Diabetes Control and Complications Trial
DL	Dose level
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
DST	Dexamethasone Suppression Test
EAP	Expanded Access Program
E/T	Early termination
ECG	Electrocardiogram/electrocardiograph
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
FT4	Free thyroxine
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GR	Glucocorticoid receptor
HBsAg	Hepatitis B surface antigen
HbA1c	Hemoglobin A1C
HDL-C	High density lipoprotein cholesterol
HDPE	High Densitiy polyethylene

HIPAA	Health Insurance Portability and Accountability Act of 1996
HHC	Home health care agency
HIV	Human immunodeficiency virus
HOMA-IR	Homeostatic Model Assessment-Insulin Resistance
HPLC/MS/MS	High pressure liquid chromatography tandem mass spectroscopy
HR	Heart rate
hsCRP	High sensitivity C-reactive protein
IC50	Half-maximal suppression (50% inhibitory concentration)
ICF	Informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IFG	Impaired Fasting Glucose
IgG	Immunoglobulin G
IGT	Impaired Glucose Tolerance
IgM	Immunoglobulin M
Imax	Maximal suppression of UFC
IPSS	Inferior petrosal sinus sampling
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-treat
IUD	Intrauterine device
Ka	Absorption rate constant
LDH	Lactate Dehydrogenase
LDL-C	Low density lipoprotein cholesterol
LLN	Lower limit of normal
L-N	Levoketoconazole-naïve cohort (or population)
LNSC	Late night salivary cortisol
LSMEAN	Least Squares Mean
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 of three 24-hour UFC samples
NCI-CTCAE	National Cancer Institute Common Terminology for Adverse Events,
NGSP	National Glycohemoglobin Standardization Program
OGTT	Oral glucose tolerance test
OLE	Open-label extension
OPTICS	Acronym for Study COR-2017-OLE, an open-label extension study
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per protocol
PT	Prothrombin time
PTT	Prothromboplastin time
QD	Once daily

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
RES	Restoration Phase
RCV	Reference change value
RW	Randomized Withdrawal Phase
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
S-C	SONICS-completer cohort (or population)
SD	Standard deviation
SONICS	Acronym for Study COR-2012-01
SPM	Study procedures manual
t½	Half-life
T2DM	Type 2 diabetes mellitus
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitors
TM	Dose Titration and Maintenance Phase
Tmax	Time of peak concentration
TSH	Thyroid stimulating hormone
UFC	Urinary free cortisol
ULN	Upper limit of normal
V/F	Apparent volume of distribution following oral administration
WBC	White blood cell

1 INTRODUCTION

1.1 Disease Background

Endogenous Cushing´s syndrome (CS) is a rare, serious and potentially lethal endocrine disease caused by chronically elevated cortisol. The incidence of CS has been estimated to be 0.7 to 2.4 cases per million per year [Sharma 2015]. The prevalence of CS has been reported to be approximately 79 cases per million [Bolland 2011]. Patients with incompletely controlled disease are seriously ill and have a higher mortality rate than age-and gender matched controls, mainly due to metabolic and cardiovascular complications [Bolland 2011, Clayton 2016, Dekkers 2013, Pivonello 2016].

Treatment options for CS include surgery, radiation therapy and medical treatment [Pivonello 2015]. Medical treatment is used to suppress excessive cortisol production or activity and ameliorate its clinical manifestations prior to surgery, while awaiting the effects of radiation therapy [Nieman 2015], or in cases when surgery is delayed, contraindicated, or unsuccessful. As such, normalization of 24-hour urinary free cortisol (UFC) is considered a reliable marker of disease remission [Bertherat 2016, Bochicchio 1995]. More recently, late night salivary cortisol (LNSC) has also been shown to reflect remission but is not yet considered to be as reliable as UFC [Amlashi 2015, Findling 2016]. Conversely, the persistence of high or only modestly reduced UFC levels argues for treatment failure, i.e. persistent disease.

Ketoconazole (Nizoral®, a true racemate comprised of two enantiomers: cis-2S,4R- and cis-2R,4S-ketoconazole) is an antifungal agent that reduces adrenal steroid production via inhibition of multiple steroidogenic enzymes, notably 11β-hydroxylase (CTYP11B1) and C17,20-lyase / 17α-hydroxylase (CYP17A1) [Engelhardt 1991, Sonino 1987, Nizoral 2013]. One publication has reported a direct effect of ketoconazole on ectopic adrenocorticotropic hormone (ACTH) secretion [Steen 1991]. Because of these properties, ketoconazole is a commonly used off-label drug for treatment of CS in the US and is approved for the treatment of CS in Europe and elsewhere [DeMartin 2006, Daniel 2015, Castinetti 2014, Nizoral 2013 Product Insert, Ketoconazole 2014 HRA Assessment Report].

Adrenal insufficiency is avoided by adjusting the dose of ketoconazole to normalize cortisol production. The most frequent adverse effects of ketoconazole are nausea, vomiting, abdominal pain and pruritus. When used orally as a treatment for fungal infection, ketoconazole has been associated with acute liver injury, typically asymptomatic elevated transaminasemia. Rarely, however, acute severe hepatotoxicity has been reported, leading the Food and Drug Administration (FDA) to caution that use of oral ketoconazole should be restricted to serious fungal infection when no suitable alternative exists (Outeiro 2016, Lo Re 2016, FDA 2016). Early markers for azole-related liver toxicities include elevations in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST), which are recommended to be monitored at regular intervals during treatment [Ketoconazole 2014 HRA Assessment Report, Nizoral 2013 Product Insert, Lake-Bakaar 1987, Lewis 1984]. In addition to its adverse effects on liver, ketoconazole has dose-related effects to prolong the ECG QT interval (Darpo 2013) and is associated with numerous potential drug-drug interactions, principally via its

inhibitory effects on certain cytochromes P450 (CYPs) responsible for xenobiotic metabolism (Nizoral 2013 Product Insert).

Cortendo AB is developing levoketoconazole, also known as COR-003, the cis-2S,4R enantiomer of ketoconazole, as an investigational new drug for the treatment of cortisol hypersecretion in CS. It is hypothesized that levoketoconazole may prove to be both safer and more efficacious than ketoconazole. Levoketoconazole has a significantly lower IC50 (50% inhibitory concentration) towards key enzymes regulating cortisol synthesis (11β -hydroxylase, IC50 = 150 nM; 17-α-hydroxylase, IC50 = 48 nM) than the 2R,4S enantiomer of ketoconazole (IC50 = 680 nM and 1800 nM, respectively), thus potentially allowing a lower dose of drug to achieve the same efficacy [Rotstein 1992, Moulder Centre, 2012]. In rats, levoketoconazole reduced corticosterone (the major glucocorticoid in rodents) more potently and effectively than either 2R,4S-ketoconazole or ketoconazole [Cortendo Report 2002-02-21].

Preclinical data suggest that levoketoconazole may pose less risk to impair hepatic function than ketoconazole. Levoketoconazole has 12-fold higher IC50 towards CYP7A (IC50 = 2.4 μM), i.e. lower potency, than does 2R,4S-ketoconazole (IC50 = 0.195 μM) [Rotstein 1992]. CYP7A is the first and rate-limiting enzyme in the major (classical) liver pathway for production of bile acids, catalyzing 7α-hydroxylation of cholesterol and other oxysterols. Inhibition of this enzyme can lead to functional cholestasis and consequent accumulation of potentially toxic metabolites such as bilirubin and xenobiotics, including ketoconazole itself. Another property that suggests potentially improved safety of levoketoconazole compared to ketoconazole relates to the pharmacokinetics (PK) of the 2S,4R- and 2R,4S-enantiomers, which have been studied in humans after oral administration of ketoconazole or levoketoconazole [Gerber 2003, Schindler 2003, Schwartz 2008]. The enantiomers of ketoconazole are present in equal amounts, but following ketoconazole oral administration plasma concentrations of the 2S,4R-enantiomer exceed those of the 2R,4S-enantiomer by approximately 3-fold [Gerber 2003], suggesting preferred extraction of the 2R,4S enantiomer by the liver. Assuming that liver injury is a function of hepatocyte exposure to drug, reduced hepatic exposure to the 2S,4R enantiomer (i.e. levoketoconazole) would be expected to be associated with reduced propensity for toxicity dose-for-dose compared ketoconazole; however, there are no published studies that directly address this hypothesis.

Levoketoconazole has been previously administered to healthy volunteers and human subjects with Type 2 Diabetes Mellitus (T2DM). Doses of levoketoconazole over the range of 200 mg to 600 mg once daily (QD) for up to 14 days and 150 mg to 450 mg for up to 4 months were shown to be generally well tolerated in these studies, with an adverse effect profile similar to ketoconazole, including sporadic cases of elevated transaminases in the Phase 2b study in T2DM.

The first pivotal clinical trial investigating the safety and efficacy of levoketoconazole in subjects with endogenous CS, Study COR-2012-01 (aka SONICS) is ongoing, having begun in 2014. This is an open-label, single-arm study with a Screening Phase, a Dose Titration Phase, a 6-month Maintenance Phase, and a 6-month Extended Evaluation Phase. SONICS enrolled 94 subjects in total. SONICS is monitored by an independent Data Safety Monitoring Board (DSMB), which reviews all serious adverse events (SAEs) and adverse events of special interest (AESI) as they are reported and meets twice yearly

to review all available efficacy and safety data. At the most recent meeting in April 2018, with the study fully enrolled, the DSMB indicated that the SONICS study should continue as planned. The current study will include subjects who have previously completed SONICS as well as subjects who have not been previously exposed to levoketoconazole.

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

1.2 Rationale for Study Design

This study, the second pivotal clinical trial investigating the safety and efficacy of levoketoconazole in subjects with endogenous CS, is a double-blind, randomized, placebo-controlled withdrawal following single-arm, open-label, trial of therapy with levoketoconazole that will assess efficacy, safety, tolerability, and PK of levoketoconazole in subjects with endogenous CS.

Randomization and blinding are used to minimize biases. A blinded-treatment Restoration Phase, in which all subjects are returned to active treatment with their Therapeutic Dose of levoketoconazole, is included for subjects who do not require early rescue and who tolerate the 8-week blinded, randomized withdrawal to completion. Masking study drug during the Restoration Phase eliminates any potential for bias introduction via knowledge of the treatment assignment in the Randomized-withdrawal Phase. An add-on of study medication (doubling the number of tablets ingested) during the blinded Restoration Phase was chosen over a direct substitute of blinded medication (holding the number of tablets ingested constant), owing to the desire to titrate the Restoration Phase medication to minimize adverse effects of rapid re-introduction of levoketoconazole. Titrating from Dose Level (DL1) during Restoration Phase could potentially result in functional unblinding of subjects assigned to receive levoketoconazole during the Withdrawal Phase.

Two populations, or cohorts, have been defined for analytical purposes: subjects who have completed all visits in SONICS through M12 (the final scheduled visit prior to safety follow-up) at any time in the past and who have been receiving a stable Therapeutic Dose throughout the 12-weeks prior to Screening, hereafter referred to as the SONICS-completer cohort, and subjects who did not participate in the prior clinical study of levoketoconazole (COR-2012-01 aka SONICS), plus subjects who completed Visit M12 of SONICS but who have not been treated with a stable Therapeutic Dose of levoketoconazole throughout the 12-week period immediately prior to Screening in the current study, hereafter known as the levoketoconazole-naïve cohort.

There is also a procedure-only distinction made between those who have completed SONICS recently (those completing within 6 months prior to screening) and distant completers of SONICS (those completing more than 6 months from screening). Distant completers of the SONICS study will need to undergo additional Screening procedures to confirm eligibility.

The concept of Therapeutic Dose originates in the parent SONICS study, wherein the Therapeutic Dose is considered established when: (a) mean UFC levels determined from a total of **four** adequate 24-hour urine collections are at or below the ULN of the central

laboratory's reference range, or (b) the maximum dose allowed has been reached, or (c) a partial UFC response has been determined and the maximal tolerated dose has been reached. Although this definition of Therapeutic Dose shall suffice for subjects who complete the SONICS study entering LOGICS, for subjects in the levoketoconazole-naïve cohort, the definition of Therapeutic Dose will be restricted to the dose of levoketoconazole associated with normalization of UFC (at or below the ULN of the reference assay) only. The choice to restrict the definition of Therapeutic Dose among subjects in the levoketoconazole-naïve cohort was determined based on the design of the current study—interpreting the effects of withdrawal from active drug is "cleaner" when the Therapeutic Dose (i.e. a prior response to therapy) is defined singularly.

The chosen design has considered the reported experience treating CS patients with ketoconazole [Castinetti 2014]. Like ketoconazole, dosing of levoketoconazole needs to be individualized, since therapeutic need varies considerably among patients. Response to therapy (e.g. as determined by reduction in UFC and improved clinical signs and symptoms) is equally variable and results in a wide range of effective doses, each tailored to an individual patient. As such, the design of this study includes a Dose-Titration and Maintenance (TM) Phase for subjects in the levoketoconazole-naïve cohort, including subjects who completed all visits in SONICS but who have not been treated with a stable Therapeutic Dose of levoketoconazole throughout the 12 weeks prior to Screening that will identify a Therapeutic Dose for each subject (see Section 4.2.2 for details).

Post-randomization, the blinded, randomized withdrawal design employs a placebo comparator to establish the efficacy and safety of levoketoconazole based on the expectation of loss of prior-established response upon administration of placebo, and maintenance of response with active treatment. The time allowance—approximately 8 weeks (maximum 9 ½ weeks)—provided for the demonstration of loss of efficacy is considered adequate based on the relationship between withdrawal of ketoconazole and loss of efficacy, as documented in published case reports and series. A longer period of withdrawal is neither necessary nor advisable, considering the higher risk of exposure to unrecognized hypercortisolemia as the withdrawal interval increases. Withdrawal to an active comparator was not considered as a practical matter, in that testing for superiority or non-inferiority to an active comparator would require a very large study size beyond the ability to recruit within a reasonable timeframe. Because of its efficiency, the randomized withdrawal design exposes a small number of subjects to placebo compared with most other designs. As an additional protection, subjects may be "rescued" with open-label treatment at any time prior to the completion of the 8-week Randomized Withdrawal phase if the Investigator determines such rescue is needed based on pre-defined criteria as set forth in Section 4.3.1.

The enrollment of subjects who have completed the SONICS study will allow for controlled assessment of the durability of efficacy of levoketoconazole beyond 1 year. The randomized-withdrawal design can provide an inference concerning the duration of drug effect based on the active-therapy period preceding the Randomized Withdrawal phase. Specifically, when the following conditions are met, the duration of preceding active therapy is inferred as the demonstrated duration of efficacy durability: (1) the duration of active therapy was verified; (2) the therapy was dispensed and used continuously (within expected normal variability in adherence), and (3) the effect of

active drug on the disease state was measured regularly using a validated biomarker or clinical outcome. In the current study, all subjects who have completed SONICS will have received levoketoconazole continuously for more than 1 year, with drug use and effect on UFC and LNSC monitored at regular intervals by the same Investigators. Therefore, if efficacy is demonstrated in the overall study population, and the efficacy trend within the SONICS-completer cohort drives the overall study population effect, it will be reasonable to infer that the efficacy of levoketoconazole is reliably durable for up to the average (or median) time of drug exposure within the SONICS-completer cohort.

2 OBJECTIVES

2.1 Primary Objective

To determine the effect of withdrawing to placebo versus continuing treatment with levoketoconazole on the cortisol therapeutic response previously established during open-label levoketoconazole therapy.

2.2 Secondary Objectives

1. To compare the effects of levoketoconazole with placebo on cortisol status (inferred from mean urinary free cortisol [mUFC] and/or late night salivary cortisol [LNSC]) during the Randomized Withdrawal Phase and the subsequent Restoration Phase;
2. To compare the effects of levoketoconazole with placebo on changes in biomarkers of CS comorbidities (fasting glucose, fasting insulin, homeostatic model assessment-insulin resistance [HOMA-IR], hemoglobin A1c [HbA1c], total cholesterol, low-density lipoprotein-cholesterol [LDL-C], and high-sensitivity C-reactive protein [hsCRP]);
3. To compare the effects of levoketoconazole with placebo on changes in health-related quality of life (QoL) and symptoms of depression;
4. To compare the effects of levoketoconazole with placebo on changes in acne, hirsutism and peripheral edema;
5. To assess the safety and tolerability of levoketoconazole;
6. To evaluate the population pharmacokinetics (PK) of levoketoconazole in subjects with CS.

NOTE: Secondary Objectives 5 and 6 are not subjects of hypothesis tests.

2.3 Exploratory Objectives

1. To assess changes in anti-diabetic, anti-cholesterol, anti-hypertensive, and chronic anti-inflammatory therapies;
2. To describe the effects and durations of levoketoconazole action with respect to cortisol status and clinical signs and symptoms of CS other than acne, hirsutism and peripheral edema;
3. To describe the dose-response relationship of levoketoconazole with respect to safety and tolerability;

4. To describe the effects of levoketoconazole on glucose tolerance among subjects with impaired fasting glucose (IFG).

3 ENDPOINTS

3.1 Primary Endpoint

Proportion of subjects with loss of therapeutic response to levoketoconazole upon withdrawing to placebo compared with the proportion of subjects with loss of therapeutic response upon continuing treatment with levoketoconazole. Loss of therapeutic response (i.e. relapse) is inferred based on mUFC from **three** 24-hour UFC measurements obtained at any visit from second through final Randomized Withdrawal Phase visits (RW1 through RW5 inclusive) when:
(1) mUFC is above 1.5X the ULN of the central laboratory's reference range, OR
(2) mUFC is more than 40% above the baseline (RW0) value, if the RW0 value is above the ULN (i.e. >1.0X ULN)[1], OR
(3) an early rescue criterion is met.

3.2 Secondary Endpoints

- Changes from Baseline (RW0) in mUFC and LNSC at all post-Baseline visits with these assessments through the final study visit (RES2)—applies to Secondary Objective 1;
- Proportion of subjects with normalization of mUFC at RES2—applies to Secondary Objective 1;
- Proportion of subjects with normalization of mUFC at the end of Randomized Withdrawal Phase—applies to Secondary Objective 1;
- Changes from Baseline (RW0) in biomarkers of CS comorbidities (fasting glucose, fasting insulin, homeostatic model assessment-insulin resistance [HOMA-IR], hemoglobin A1c [HbA1c], total cholesterol, low-density lipoprotein-cholesterol [LDL-C], and high-sensitivity C-reactive protein [hsCRP]) at all post-Baseline visits with these measurements through the final study visit (RES2)—applies to Secondary Objective 2;
- Changes from Baseline (RW0) in health-related QoL and symptoms of depression at all post-Baseline visits with these assessments through the final study visit (RES2)—applies to Secondary Objective 3;
- Changes from Baseline (RW0) in acne, hirsutism and peripheral edema at all post-Baseline visits with these assessments through the final study visit (RES2)—applies to Secondary Objective 4;
- Incidence and severity of adverse events (AEs), particularly adverse events of special interest (AESIs) during levoketoconazole open-label therapy in the TM

[1] This category applies only to subjects who have completed SONICS, who may have a Therapeutic Dose established with UFC above the ULN of the reference range. Levoketoconazole-naïve subjects must have UFC at or below the ULN at RW0 to qualify for randomization.

Phase (levoketoconazole-naïve cohort) and during blinded therapy in the Randomized Withdrawal Phase and Restoration Phase (both cohorts)—applies to Secondary Objective 5.

3.3 Pharmacokinetic Endpoints and Pharmacokinetic/Pharmacodynamic Modeling

- Estimates of the following PK parameters: clearance (CL/F), volume of distribution (V/F), absorption rate constant (Ka), with associated between-subject variability where feasible. These parameters will be used to calculate half-life (t½), area under the concentration time curve (AUC) and peak concentration (Cmax), if feasible—applies to Secondary Objective 6;
- Estimates of the following pharmacodynamic (PD) parameters: levoketoconazole concentration producing half maximal UFC suppression (IC50), maximal suppression of UFC (Imax) and associated estimates of between-subject variability, if feasible. UFC concentrations in relation to dose and plasma exposure will be explored—applies to Secondary Objective 6.

3.4 Exploratory Endpoints

- Frequency of usage and changes from Baseline (RW0) in frequency of usage of anti-diabetic, anti-cholesterol, anti-hypertensive, and chronic anti-inflammatory therapies at all post-Baseline visits; changes in corresponding biomarkers accounting for changes in medication usage will also be explored—applies to Exploratory Objective 1;
- Time from RW0 to first time of loss of response, when:
  (1) mUFC is above 1.5X the ULN of the central laboratory's reference range, OR
  (2) mUFC is more than 40% above the RW0 value, if the RW0 value is above the ULN (i.e. >1.0X ULN)[2], OR
  (3) an early rescue criterion is met—applies to Exploratory Objective 2;
- Time to first normalization of mUFC beginning from RW5 (subset with mUFC above 1.5X ULN at RW5)—applies to Exploratory Objective 2;
- Time to first normalization of LNSC beginning from RW5 (subset with LNSC above ULN at RW5) —applies to Exploratory Objective 2;
- Proportion of subjects with normalization of mUFC at the end of Dose Titration and Maintenance Phase (TM7)—applies to Exploratory Objective 2;
- Proportion of subjects with either normalization of mUFC or partial response (at least 50% decrease in mUFC) at the end of Dose Titration and Maintenance Phase (TM7)—applies to Exploratory Objective 2;

[2] This category applies only to subjects who have completed SONICS, who may have a Therapeutic Dose established with UFC above the ULN of the reference range. Levoketoconazole-naïve subjects must have UFC at or below the ULN at RW0 to qualify for randomization.

- Proportion of subjects with normalization of LNSC at RES2—applies to Exploratory Objective 2;
- Changes from Baseline (RW0) in serum cortisol and ACTH at all post-Baseline visits with these assessments through the final study visit (RES2)—applies to Exploratory Objective 2;
- Changes from Baseline (RW0) in clinical signs and symptoms of CS excluding acne, hirsutism and peripheral edema at all post-Baseline visits with these assessments through the final study visit (RES2)—applies to Exploratory Objective 2;
- Frequency and severity of common AEs and laboratory abnormalities in relation to dose of study drug administered at the time of the reported AE or laboratory abnormality—applies to Exploratory Objective 3;
- Shifts from normality and concentration changes from Baseline (RW0) in serum transaminases, alkaline phosphatase (AP), and total bilirubin at all post-Baseline visits in relation to dose of study drug administered at the time of the shift or change—applies to Exploratory Objective 3;
- Durations and changes in durations from Baseline (RW0) of the QTc interval in relation to dose of study drug administered proximal to the measurement—applies to Exploratory Objective 3.
- Change from Baseline in observed and derived glucose and insulin parameters during oral glucose tolerance test (OGTT) in the subset of subjects with IFG—applies to Exploratory Objective 4.

4 STUDY DESIGN

4.1 Overview of Study Design

This is a double-blind, randomized, placebo-controlled withdrawal and restoration (or as-needed early rescue) study in subjects with endogenous CS previously treated with single-arm, open-label levoketoconazole that will assess efficacy, safety, tolerability, and PK of levoketoconazole.

Two populations or cohorts, are defined for analytical and procedural purposes, levoketoconazole-naive and SONICS-completer, defined as follows:

Levoketoconazole-naïve cohort: Subjects who did not participate in the prior clinical study of levoketoconazole (COR-2012-01, aka SONICS) **plus** subjects who completed Visit M12 of SONICS (final scheduled visit prior to safety follow-up) but who have not been treated with a Therapeutic Dose of levoketoconazole throughout the 12-week period immediately prior to Screening in the current study.

SONICS-completer cohort: Limited to subjects who have completed all visits in the SONICS study through M12 (final scheduled visit prior to safety follow-up) at any time prior to the current study **and** who have been treated with a stable Therapeutic Dose of levoketoconazole throughout the 12-week period immediately prior to Screening. (Note:

A stable dose is defined as a Therapeutic Dose that has been received by the subject for 12 weeks without requiring a change in dose.)

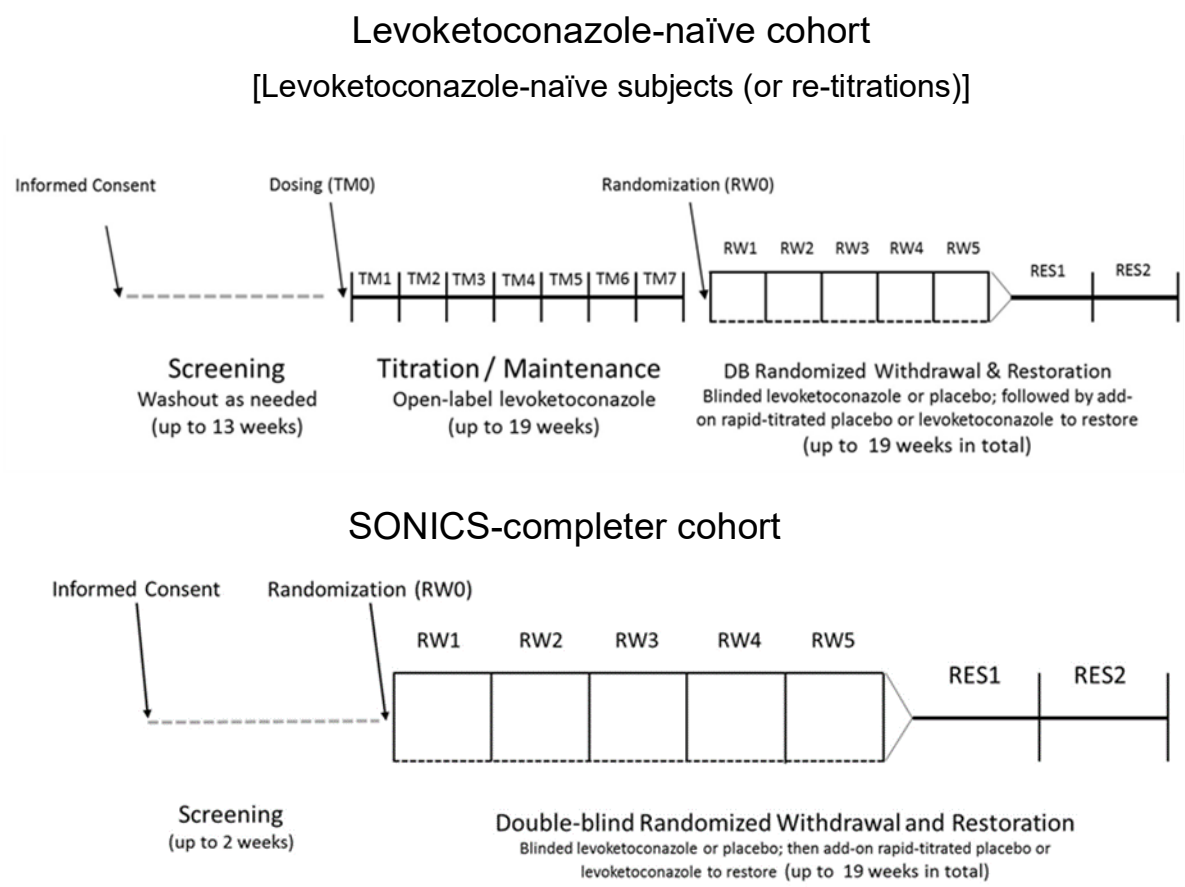
Subjects completing all visits in SONICS who have not been treated with a Therapeutic Dose of levoketoconazole throughout the 12-week period immediately prior to Screening must re-establish their Therapeutic Dose in the TM Phase as part of the levoketoconazole-naïve cohort. Subjects re-establishing the Therapeutic Dose via re-titration may begin titration at their current or next higher level most recently received at the discretion of the Investigator. However, all SONICS subjects re-titrating must follow the 14-week minimum Dose Titration and Maintenance schedule.

Study methodology varies by cohort prior to randomization (RW0) only. Following initial Screening (washout as necessary) and Dose Titration and Maintenance phases, as applicable, this study will be conducted in two randomized, double-blind treatment phases (a Randomized Withdrawal Phase and a Restoration Phase). The overall design and the designs for each cohort are described and schematized in Table 1 and Figure 1 below.

Table 1 Study Design

Open-label levoketoconazole	Therapeutic Dose established in Dose Titration and Maintenance (TM) Phase for levoketoconazole-naïve cohort, or prior to entry into LOGICS for the SONICS-completer cohort	
Randomization (RW0)	⇩	⇩
Blinded Randomized Withdrawal Phase	**Levoketoconazole** at Therapeutic Dose	**Placebo** at equivalent tablet count to Therapeutic Dose
Blinded Restoration Phase	**Placebo** added as 1 tablet twice daily (BID) at RW5 then add 1 tablet every 2 days, alternating AM and PM, until the total tablet count is double the count at RW0	**Levoketoconazole** added as 1 tablet BID at RW5 then add 1 tablet every 2 days, alternating AM and PM, until the total tablet count is double the count at RW0

Figure 1 Study Design Schematics



Note: RW5, the last visit of the Randomized Withdrawal Phase marks the start of the Restoration Phase

NOTE: If there is a time gap between completion of Screening and TM0 or RW0 for subjects currently receiving levoketoconazole, then open-label levoketoconazole should be continued between Screening and TM0 or RW0 to maintain the Therapeutic Dose. If rolling over from SONICS, subjects will be dispensed LOGICS medication starting at the screening visit. If entering from the expanded access program (EAP), subjects will stay on open-label levoketoconazole dispensed from EAP until the Baseline visit.

- **Screening Phase**: For the levoketoconazole-naïve cohort, screening duration may last up to approximately 13 weeks to allow for as-needed wash out of Cushing's syndrome medications. For the SONICS-completer cohort, screening duration is estimated to be 2 weeks and may begin concurrently with Visit M12; see Sections 4.2.1 and 4.2.2 for details.
- **Dose Titration and Maintenance Phase (TM Phase) [levoketoconazole-naïve subjects and re-titrations ONLY]**: Duration is a minimum of 14 weeks and up to approximately 19 weeks to achieve an effective and tolerable dose of levoketoconazole (i.e. the Therapeutic Dose); see Section 4.2.2.2 for details. Note that subjects who completed SONICS but are being treated as part of the levoketoconazole-naïve cohort (see above) and must re-titrate, must complete at least 14 weeks of dose titration and

maintenance, regardless of the duration needed to re-establish their Therapeutic Dose according to the LOGICS definition.

- **Double-blind, Randomized Withdrawal Phase (RW0-RW5; all eligible subjects):** Duration is approximately 8 weeks (maximum 9½ weeks) to evaluate the efficacy and safety of continued treatment with the established Therapeutic Dose of levoketoconazole compared to withdrawal to a matched placebo (administered in same regimen as the established Therapeutic Dose). Early rescue criteria are established to provide immediate use of active medication (open-label levoketoconazole) at any time during this phase if the subject's clinical condition warrants it; see Section 4.3 for details.
- **Double-blind, Restoration Phase (RW5-RES2; all eligible subjects):** Duration is approximately 8 weeks (maximum 9½ weeks). To maintain the blind and ensure subjects are managed at their established Therapeutic Dose, subjects will be additionally dosed with either placebo or levoketoconazole until the addition of tablets equals the original levoketoconazole tablet count (i.e. total tablet count will be twice the tablet count of levoketoconazole at the established Therapeutic Dose). Specifically, for those subjects randomized to placebo during the Randomized Withdrawal Phase, levoketoconazole will be added during Restoration Phase, and for those subjects randomized to levoketoconazole, matched placebo will be added during Restoration Phase see Section 4.4 for details.

The longest anticipated exposure to active study medication is no more than approximately 38 weeks and the shortest approximately 8 weeks; these exposure durations exclude any exposure in SONICS or in an EAP. If rolling over from SONICS, subjects will be dispensed LOGICS medication during screening phase which should be no more than 11 (±3) days. If entering from EAP, subjects will stay on open-label levoketoconazole dispensed through EAP during the screening phase which should be no more than 11 (±3) days. The longest anticipated exposure to placebo monotherapy is no more than 9½ weeks, with provisions for earlier rescue with active drug in case of decompensation. The longest anticipated total study participation duration is approximately 51 weeks.

Efficacy will be assessed by measuring UFC levels and other endpoints at the times indicated in the Time and Events Schedules (Appendix A).

Blood samples for PK determination will be collected as described in Section 6.4.7.1. Note that the times indicated in the Time and Events Schedules (Appendix A) are indicative of potential collection times.

Safety data will be collected at the times indicated in the Time and Events Schedules and as described in Section 6.4.

Adequate medical coverage shall be provided by the Investigator throughout 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 site's medical staff regardless of day and time to obtain medical care.

An independent DSMB will review key safety data throughout the study. The DSMB will be composed of experts in aspects of drug safety and benefit-risk assessment germane to the therapeutic area and the known safety issues associated with levoketoconazole (e.g. liver injury, QT prolongation).

All subjects who complete the study, where completion is defined as having completed Visit RES2 in the Restoration Phase OR having required use of early rescue with open-label levoketoconazole during the Randomized Withdrawal Phase, will be eligible to enter an open-label extension (OLE) study (Study COR-2017-OLE, aka OPTICS) to allow open-label treatment with levoketoconazole and assess its long-term effects on efficacy and safety. The OPTICS study is described in a separate protocol. Subjects who are not eligible for or who do not consent to participate in the OPTICS study or the EAP for levoketoconazole will be promptly referred to their endocrinologist (if not the Investigator) for further management.

Early rescue procedures and visit schedule will mimic those described for the rapid titration during the Blinded Restoration Phase (Section 4.4), except that therapy will be administered as open-label therapy, assuming the Investigator determines open-label therapy with levoketoconazole remains in the best interests of the subject. It should be noted that during the early rescue period, as treatment is open-label, dose adjustments may be made as medically indicated. This includes adjustments to dose levels above the previous therapeutic dose if required to return subject to eucortisolemia.

4.2 Pre-Randomization

4.2.1 SONICS-Completer Cohort Screening Phase

All subjects on levoketoconazole from SONICS or the EAP must have confirmation of their Therapeutic Dose, as defined in the SONICS protocol, during the Screening Phase to confirm cohort placement for LOGICS. During this time, subjects will continue their prescribed dose of levoketoconazole to ensure continuity of treatment. Subjects who have completed all visits in SONICS, through Visit M12 and have been on a stable Therapeutic Dose throughout the 12-week period immediately prior to signing informed consent, will enter the Screening Phase to confirm eligibility.

For subjects who have completed SONICS within 6 months prior to screening for LOGICS, the Screening Phase, relying primarily on data collected during SONICS and completed with data collected in LOGICS, will begin after Visit M12 of SONICS completion and end once eligibility is confirmed. The time from confirmation of eligibility to RW0 should be no more than 11 (+3) days later (the minimum time requirement for Therapeutic Dose confirmation as dictated by tolerability and UFC results). As data collected from the SONICS study will be used in this study as well, overlapping assessments only needs to be performed once (e.g. the same vital signs data may be recorded in the eCRFs for both studies).

For subjects who have completed SONICS more than 6 months prior to the Screening Phase, the screening procedures will mimic those for the levoketoconazole-naïve subjects to confirm eligibility for the current study (see inclusion criteria in Section 5). After eligibility has been confirmed during the Screening Phase, subjects should proceed

directly to the Baseline/Randomization Visit (RW0). The time between Screening and RW0 should be no more than approximately 11±3 days.

4.2.2 Levoketoconazole-Naïve Cohort

4.2.2.1 Screening Phase for Levoketoconazole-naïve Cohort

Following consent signature, subjects naïve to levoketoconazole receiving previous CS medical therapies or other prohibited medications must enter a washout period (see Section 5.2) before completing the screening assessments detailed in the Time and Events schedule (Appendix A). The Screening Phase will last up to approximately 13 weeks. Baseline measurements will be obtained as part of the Screening assessments; therefore, the time from confirmation of eligibility to TM0 (aka baseline) should be no more than 11 (+3) days. Screening procedures completed within 3 weeks of TM0 (within 2 weeks for LNSC, QTc interval and liver safety tests) will be used as the TM0 value. If Screening procedures were completed more than 3 weeks prior to TM0, then they will be repeated at TM0, (except for pituitary magnetic resonance imaging (MRI), which may be completed up to 6 months prior to TM0 or RW0). All blood samples (except for post dose PK samples) should be obtained prior to administering the first dose of levoketoconazole.

Likewise, the final Baseline UFC specimen must be collected close to the date of TM0 and never more than 6 weeks prior to TM0 (**NOTE:** all Baseline UFC and LNSC values must be obtained after washout of any medications (except levoketoconazole) that are known to influence cortisol).

If a subject does not meet the eligibility requirements described in Section 5 on initial Screening, they may be eligible to re-screen **only** if worsening of their medical condition has increased the likelihood that they would meet the study eligibility criteria. Such re-screenings will be exceptional circumstances, and all re-screenings require prior permission of the study Medical Monitor before they begin. Repeating a Screening test (e.g. UFC) that has been found to be technically flawed will not be considered re-screening.

For subjects who have completed Visit M12 in SONICS either within 6 months or more than 6 months prior to the Screening Phase and are NOT on a stable Therapeutic Dose throughout the previous 12-week period, screening procedures will mimic those for the levoketoconazole-naïve subjects as noted above to confirm eligibility and progress the subject into the TM Phase of the study as indicated in Section 4.2.2.2. In such cases, the latest available data from SONICS (e.g. Visit M12 or the Follow-up Visit) may be applied to the LOGICS Screening Visit.

4.2.2.2 Dose Titration and Maintenance Phase (levoketoconazole-naïve cohort only)

After confirmation of eligibility, subjects in the levoketoconazole-naïve cohort (including subjects that completed SONICS but require re-titration) will enter the TM Phase. The first dose of open-label therapy for this phase will be at TM0. Subjects who did not

complete Visit M12 of SONICS will always begin titration at Dose Level 1 (150 mg BID).

Subjects who have completed Visit M12 in SONICS who have **not** been treated with a Therapeutic Dose of levoketoconazole throughout the 12-week period immediately prior to Screening must also re-establish a Therapeutic Dose and remain in the TM Phase for the full 14-week period, regardless of the duration needed to establish their Therapeutic Dose for this study (i.e. even if it takes less than 14 weeks). As stated earlier, these subjects are considered as part of the levoketoconazole-naïve cohort for this study, despite not being naïve to levoketoconazole in the strict sense at the time of entry in the current study. Note that subjects in this category may begin dose-titration at their current or most recently received dose of levoketoconazole, rather than Dose Level 1, at the discretion of the Investigator.

Dose titration will occur in increments of 150 mg over a period of approximately 3 to 19 weeks to achieve an effective and tolerable dose (the Therapeutic Dose). Dose increases (and decreases, as needed) will be based on subjective and objective indicators of medication tolerance, UFC and other cortisol measures (see Section 4.2.2.2.1).

In exceptional situations, subjects may require additional time (i.e. greater than 19 weeks) to achieve the Therapeutic Dose. These situations must be approved on a case by case basis by the Medical Monitor.

Subjects must return to the clinic at least every 14 (± 3) days during the TM Phase (note: to allow for 4 weeks maintenance, additional time may be required in the event a dose change is required at TM7). However, several additional safety checks, which may be performed outside the clinic, will also be scheduled: (1) 5 days (± 2 days) after the first dose (DL1) and after dose escalations to DL2 and DL3 during the TM Phase (if needed), subjects will be contacted by site personnel remotely (e.g. by phone or email) to inquire about the subject's condition and note any adverse events. (2) If the total daily dose is escalated to 750 mg (DL4) or above, subjects will be asked to return to the clinic or, optionally, will be visited by a qualified home healthcare (HHC) professional for one extra safety evaluation to occur 5 days (± 2 days) after each dose escalation.

Subjects will be advised to contact the Investigator immediately in the event of AESI-suggestive signs or symptoms (see Section 13.2.2) regardless of the onset timing relative to a scheduled visit.

Once the Therapeutic Dose has been reached and confirmed from the mean of **three** adequately collected 24-hour urine specimens for UFC measurements (i.e. from mUFC), subjects will continue that Therapeutic Dose (i.e. remain in Maintenance) until the final open-label study visit (Visit TM7) in the TM Phase, which shall be a minimum of 14 weeks from TM0. During the TM Phase (while treatment is open-label), once the Therapeutic Dose is achieved, the dose should generally not be further adjusted if the UFC levels are within normal limits. However, the dose may be increased if medically necessary to maintain eucortisolemia or decreased to address drug intolerance or AE.

Prior to the final open-label visit (Visit TM7), **three** adequate 24-hour urine specimens will again be obtained (NOTE: collections need not be repeated if the final open-label visit coincides with the initial establishment of UFC normalization) to confirm

maintenance of UFC normalization prior to randomization, denoting UFC-eligibility for the Randomized Withdrawal Phase. To ensure the TM Phase occurs within the allotted timeframe of no more than approximately 19 weeks, urine collections should ideally be made on sequential days and prior to the actual scheduled visit for dose assessment, as results are needed to determine if dose escalation is required, or whether a confirmatory UFC is needed to establish Therapeutic Dose. The minimum duration of this phase and thus establishment of the Therapeutic Dose will be no less than approximately 14 weeks, even among subjects who reach a Therapeutic Dose more quickly. Randomization (RW0) should occur as soon as possible after the final TM Phase visit (TM7) and no more than 11 (+3) days later unless a dose change was required at Visit TM7. Regardless, in all cases, at least 4 weeks should elapse between reaching the Therapeutic Dose and RW0 to ensure tolerability and stability (continued effectiveness) of the Therapeutic Dose.

Subjects still in the TM Phase when the randomization target (approximately 46 to 54 subjects, depending on the observed withdrawal rate trend in the Randomized Withdrawal Phase) is reached, will be offered the opportunity to join the OPTICS study to receive open-label treatment. While randomization is still open, non-responders may also be eligible for OPTICS only if they achieve a partial UFC response, do not expect to require additional medication other than levoketoconazole to control cortisol, and levoketoconazole is well tolerated. Subjects must meet the OPTICS inclusion/exclusion criteria to be eligible.

4.2.2.2.1 Dose Titration and Adjustment Criteria

Levoketoconazole will be administered BID beginning at TM0 per the titration scheme in Table 2 until **one** of the following criteria has been met:

- Mean 24-hour UFC levels no higher than ULN as established for the assay being used at a central laboratory;
- Highest protocol-specified dose (i.e. DL7) reached;
- Highest tolerated dose reached (in the opinion of the Investigator).

Table 2 Dosing Titration Scheme

Dose Level (DL)*	Morning dosing	Evening Dosing
DL1	150 mg	150 mg
DL2	150 mg	300 mg
DL3	300 mg	300 mg
DL4	300 mg	450 mg
DL5	450 mg	450 mg
DL6	450 mg	600 mg
DL7	600 mg	600 mg

*DL0, permitted for dose reductions, is a dose of 150 mg QD administered in the evening, except on the day of the in-clinic or at-home visit procedures, when the dose should be administered during the visit (see Section 8.3.2).

All subjects will be asked to collect **two** adequate 24-hour urine specimens for UFC measurements prior to their next scheduled visit that will be used to determine the need for continued dose titration. The first 24-hour urine collection will be on Day 8 (± 2 days) and the second collection will be on Day 9 (± 2 days) after start of each dose level. Subjects should be asked to bring or, preferably, ship per courier service, their **two** urine collections to the clinic, as soon as possible (by approximately Day 10) for measurement of 24-hour UFC levels from each sample. The UFC results are needed prior to the next scheduled visit in order to determine the need to escalate dose. Urine volume and creatinine will be measured as markers of the adequacy of each collection (see Section 6.4.5.1 for definition). Subjects will continue their current dose of levoketoconazole until the UFC results have been obtained from the central laboratory (expected within 2-4 days of shipment) and reviewed by the Investigator. Subjects should be contacted as soon as feasible after the results from the **two** 24-hour urine samples are received. Based on these UFC results and reported tolerability to levoketoconazole, subjects will be asked to do **one** of the following:

- If UFC exceeds the ULN of the central lab reference range: Return to the clinic for scheduled assessments and, as applicable, receive the first dose of drug for the next Dose Titration interval; OR
- If UFC is at or below the ULN of the central lab reference range: Collect **one** additional 24-hour urine sample for confirmatory UFC testing to determine if the Therapeutic Dose of levoketoconazole has been reached; Section 4.2.2.2.2).

4.2.2.2.2 Determination of the Therapeutic Dose of Levoketoconazole

When normalized UFC results from the mean of the first **two** adequately collected 24-hour urine samples are returned, one **additional** 24-hour urine sample will be collected and returned to the clinic for submission to the central laboratory. The UFC results must be received prior to the actual scheduled visit, as they are needed to determine if dose escalation is required. The mean of the **three** UFC results will be used to determine if UFC normalization has occurred.

A Therapeutic Dose will be considered established only when the mUFC levels are no higher than the ULN of the assay (i.e. mUFC has been normalized). Once the Therapeutic Dose has been reached the subject should continue with that dose (i.e. in Maintenance) until the end of the TM Phase of the study (Visit TM7). During the TM Phase (while treatment is open-label), once the Therapeutic Dose is achieved, the dose should generally not be further adjusted if the UFC levels are within normal limits. However, the dose may be increased if medically necessary to maintain eucortisolemia or decreased to address drug intolerance or AE. The Therapeutic Dose must be stable (i.e. fixed), with normal mUFC established, for at least 4 weeks before a subject may be eligible for the Randomized Withdrawal Phase.

Detailed Steps for Determination of Therapeutic Dose

- If the mean value of UFC from at least **two** (up to three if indicated by the first two tests being no higher than ULN—see below) adequate 24-hour urine collections is **greater than the ULN** of the central lab's reference range, the subject should continue to dose-escalate by 150 mg approximately once every 2 weeks until a

Therapeutic Dose, a maximally tolerated dose, or maximally allowed dose (DL7) is reached.

- If the mean value for the first **two** UFC tests from two adequate 24-hour urine collections is **at or below** the ULN from the central laboratory's reference range, the subject should be notified immediately and asked to begin the **additional** 24-hour urine collection as soon as possible to confirm a biochemical response by mUFC normalization. When UFC response-confirmatory urine sample collection is required, the subsequent visit should be scheduled no later than 18 (± 3 days) days after the prior dose-escalation visit. Investigators must ensure that the subject has an adequate supply of levoketoconazole to cover the duration between visits. Refer to the Study Procedures Manual (SPM) for other confirmatory urine collection-day guidelines.
- All subjects who achieve a Therapeutic Dose, evidenced by the mean of **three** UFC values at or below the ULN, must complete all 7 TM Phase visits regardless of the Therapeutic Dose. Thus, the total duration of the TM Phase should not be less than 14 weeks and should not exceed approximately 19 Weeks. In exceptional situations, subjects may require additional time (i.e. greater than 19 weeks) to achieve the Therapeutic Dose. These situations must be approved on a case by case basis by the Medical Monitor.

Failure to Achieve Therapeutic Dose

If the subject has reached the highest allowed (i.e. DL7) or highest tolerated dose level and mUFC levels remain greater than the ULN of the central laboratory's reference range, the subject will be considered a non-responder, will not be eligible for randomization (RW0) and should be withdrawn from the study. Non-responders may be eligible for OPTICS only if they achieve a partial UFC response, do not expect to require additional medication other than levoketoconazole to control cortisol, and levoketoconazole is well tolerated.

4.2.2.3 Safety Factors to be Considered During the Dose Titration Phase

4.2.2.3.1 Possible Prolongation of QTc Interval

Subjects will have electrocardiogram (ECG) evaluations at Baseline (Visit TM0) and within approximately 1 to 2 hours after each monitored drug administration during the TM Phase, ideally using the provided Spaulding ECG device (Section 6.4.3). If persistent levoketoconazole-related QTc interval prolongation is observed (value above 500 msec or more than 60 msec increase from Baseline TM0), study medication will be temporarily held and/or the dose level reduced. Refer to Section 5.4.1 and Appendix O, where guidance to the Investigator for assessing apparently prolonged QTc interval is provided in detail. In all cases, a PK sample should be collected as close to the time of the event as possible.

4.2.2.3.2 Possible Adrenal Insufficiency

If the subject develops signs and/or symptoms of adrenal insufficiency (e.g., hypoglycemia, hyperkalemia, orthostatic hypotension, nausea, vomiting, abdominal pain), based on further investigation (see Section 6.5.3 and Appendix O for assessment of

signs and symptoms of adrenal insufficiency) and clinical judgment, the Investigator may temporarily interrupt study medication to allow resolution. In such cases, at the discretion of the Investigator, the dose will be restarted at the preceding dose level. When adrenal insufficiency is observed at DL1, subjects may be provided a lower dose of **150 mg QD (DL0)** following agreement with the Sponsor. Subjects may resume the Dose Titration scheme after a dose reduction at the discretion of the Investigator and agreement of the Sponsor. In all cases, a PK sample should be collected as close to the time of the event as possible.

4.2.2.3.3 Possible Liver Injury

Criteria have been developed to guide the Investigator towards frequent monitoring, temporary drug interruption, dose reduction, rechallenge, or permanent study medication cessation and study withdrawal in cases when liver injury is suspected or confirmed.

Recommendations from the FDA Guidance on Drug-Induced Liver Injury: Premarketing Clinical Evaluation (July 2009) have been adopted for use in this study to monitor for evidence of early liver injury. Per FDA guidance, discontinuation of investigational therapy should be considered in the case of:

- 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** total bilirubin above 2X ULN or International Normalized Ratio (INR) above 1.5 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;
- 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 total bilirubin above 2X ULN in the absence of evidence for obstruction or Gilbert syndrome. NOTE: An ultrasound evaluation of the gallbladder and bile duct should be conducted to exclude cholestasis as the cause for elevated AP and/or total bilirubin.
- Not included in FDA guidance but additionally specified for this study as a finding that should prompt evaluation and possible action: Subjects with ALT or AST above 3X ULN or AP above 2X ULN (in the absence of evidence for cholestasis) or total bilirubin above 2X ULN (in the absence of evidence for cholestasis and except for subjects enrolled with presumed Gilbert's syndrome).

The above criteria are also found in Section 5.4.2. and Appendix O, which describes considerations for study withdrawal due to suspected or confirmed drug-induced liver injury.

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.

The need for levoketoconazole interruption will be influenced by the Baseline (TM0 for levoketoconazole-naïve) 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 to 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 total bilirubin 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 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 total bilirubin, 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.

In all cases, a PK sample should be collected as close to the time of the event as possible. If abnormally elevated liver safety tests return near to the subject's 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 O).

Rechallenge with Study Medication

If levoketoconazole dosing has been interrupted and liver safety tests normalize, subjects may be re-challenged (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 re-check 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.

4.2.2.3.4 Stopping Criteria During Dose Titration and Maintenance

Dosing with study medication will cease permanently due to any of the following observations:

- Intolerability to the study medication based on the subjects' signs or symptoms in accordance with the Investigator's medical judgment;

- Lack of clinically relevant response at the maximally tolerated dose, in the opinion of the Investigator;
- QTc prolongation as specified in Section 5.4.1 at 150 mg/day;
- Liver safety test abnormalities as specified in Section 5.4.2;
- Adrenal insufficiency at the lowest dose of study medication (equivalent to 150 mg daily)—See Sections 5.4.3 and 6.5.3 for details;
- Any withdrawal criteria met as specified in Section 5.4.

4.2.2.4 Dose Titration at 750 mg/day or Above

The safety of levoketoconazole at doses 750 mg/day or above is less established than at lower daily doses. For this reason, in addition to the assessments that are carried out at each dose-escalation, subjects that reach total daily doses of 750, 900, 1050, and 1200 mg/day (dose levels DL4 to DL7) will be asked to return to the clinic or will be visited by a qualified HHC professional for one extra safety evaluation 5 days (± 2 days) after each dose escalation to include the following assessments: AEs, vital signs, routine safety laboratory assessments (including liver safety tests), ECGs and morning serum cortisol levels, as outlined in Time and Events Schedule (Appendix A) and in Section 6.4.6.1. Subjects should also be advised to contact the Investigator immediately in the event of suspected adrenal insufficiency (see Section 6.5) or other AEs between high-dose titration visits.

Consult Section 4.2.2.2.2 for determination of the Therapeutic Dose via confirmatory urine collection for UFC, which is the same for the high-dose range.

4.2.2.5 Transition from Dose Titration and Maintenance (TM) Phase to Randomized Withdrawal Phase

Eligibility for entering the Randomized Withdrawal Phase requires the levoketoconazole-naïve cohort subjects to have established and maintained a Therapeutic Dose for at least 4weeks as confirmed by the average of UFC values with results received prior to the RW0 Visit. Prior to the final open-label visit in the Dose Titration and Maintenance (TM) Phase (Visit TM7), **three** complete 24-hour urine specimens will be obtained (collections need not be repeated if the final open-label visit coincides with the initial establishment of UFC normalization, i.e. Therapeutic Dose) to confirm UFC-eligibility for the Randomized Withdrawal Phase. Randomization (RW0) should occur as soon as possible after the final Titration-Maintenance visit (TM7) and no more than 11 (+3) days later unless a dose change was required at Visit TM7. At least 4 weeks should elapse between reaching the Therapeutic Dose and RW0 to ensure tolerability and stability of effectiveness.

4.3 Randomized Withdrawal Phase (All Subjects)

In order to qualify for randomization, ALL subjects must have established and maintained a Therapeutic Dose for at least 4 weeks as confirmed by the average of 3 UFC values with results received prior to the RW0 Visit.

All eligible subjects (from both the SONICS-completer and levoketoconazole-naïve cohorts) will enter the 8-week, double-blind Randomized Withdrawal Phase. At this point in the study, SONICS-completer and levoketoconazole-naïve cohorts are treated identically. In the Randomized Withdrawal Phase, subjects will return to the clinical site at least twice: on RW3 {Day 30 (-4)} and RW5 {Day 58 (-4)} relative to the Randomization Visit (RW0) for safety and efficacy evaluations, to determine if they are still responding to therapy (i.e. have maintained mUFC within normal range or, for certain SONICS-completer cohort subjects, within previously established therapeutic range) or if they have partial loss of response or relapse, as defined in Section 4.3.1.

In addition, all subjects will complete **three** further visits either at-home (by a qualified HHC professional) or on-site (if qualified HHC professional is unavailable or not allowed/preferred) on RW1 {Day 10 (-2)}, RW2 {Day 20 (-2)} and RW4 {Day 40 (-2)} relative to Randomization (RW0). These interim visits will be primarily for determining cortisol status as well as to monitor safety and tolerability associated with the possible withdrawal of medication. Although UFC will be the primary measure determining loss of therapeutic efficacy, cortisol status will also be assessed through additional measures, including LNSC. Partial loss of response or relapse should be confirmed by a repeat (i.e. **one additional**) 24-hour urine sample (or LNSC sample), which should be collected and analyzed as soon as possible after the preliminary mUFC value is known. Courier services will be provided, as desired, to collect UFC and LNSC specimens for transport to the site on days when a qualified HHC professional is not present or if subjects prefer courier pickup of collected samples prior to visit (Appendix A).

Early-rescue criteria are described that provide for **immediate** substitution of blinded study drug with open-label levoketoconazole treatment directed by the study Investigator whenever continued use of blinded treatment in the Randomized Withdrawal Phase is regarded as unacceptable owing to significant or rapid clinical deterioration. Criteria to guide the Investigator as to the possible need for early rescue medication are described in Section 4.3.1.

4.3.1 Early Rescue Criteria and Procedures

Early rescue is a key safety component of the study that is intended to protect subjects from experiencing disease-related morbidity should they experience a documented loss of therapeutic effect at **any time** during the Randomized Withdrawal Phase. It is anticipated that at least several subjects who are randomized to receive placebo will require early rescue treatment prior to completion of the Randomized Withdrawal Phase. Before proceeding with early rescue, the Principal Investigator must discuss with the Medical Monitor. If early rescue is needed, such subjects will be deemed Study Completers and may be considered as eligible for enrollment in the long-term OPTICS study or for EAP if they otherwise qualify. If early rescue is deemed appropriate with open-label levoketoconazole, subjects continue in the study using Blinded Restoration Phase procedures described in Section 4.4. Subjects requiring rescue medication should complete all procedures for visit RW5 prior to entering the Restoration Phase (see Table 9).

Early rescue procedures and visit schedule will mimic those described for the Blinded Restoration Phase (Section 4.4), except that therapy will be administered as open-label

therapy, assuming the Investigator determines open-label therapy with levoketoconazole remains in the best interests of the subject. The rapid titration schedule used in the Restoration Phase should be used to reestablish the Therapeutic Dose if a subject requires early rescue with open label levoketoconazole. During early rescue, the titration will increase in 1 tablet increments every 2 days alternating AM and PM per Table 2. As treatment is open-label during early rescue, dose adjustments may be made, as medically indicated. This includes adjustments to dose levels above the previous therapeutic dose if required to return the subject to eucortisolemia. Blinding to the treatment code should be maintained as described in Section 8.3.3.1, so as not to reveal the dosing assignment made during Randomized Withdrawal. If the subject and Investigator choose to administer a treatment other than levoketoconazole as early rescue therapy, such treatment will be administered outside of the study (i.e. the subject must be withdrawn from the study at that time).

Subjects who require and choose early rescue with open-label levoketoconazole will undergo RW5 procedures (Table 9) immediately prior to administration of open-label drug (except ECG to be done 1-2 hours after administration of rescue medication).

Early rescue during the Randomized Withdrawal Phase must be considered when a subject demonstrates one or more of the following criteria at any time after randomization:

1. Relapse of hypercortisolemia (i.e. loss of therapeutic response). Defined as:
    - mUFC from **three** urine collections that is above 1.5X ULN

    OR

    - mUFC from **three** urine collections that was above 1X ULN at Baseline (RW0) and increases by more than 40% above the baseline value for SONICS-completer cohort subjects.

    NOTE: Relapse as per UFC criterion should always trigger early rescue as soon as it is observed
2. Partial loss of cortisol response. Defined as:
    - mUFC from **three** urine collections that increases from Baseline (RW0) to greater than 1X ULN but no more than 1.5X ULN

    OR

    - LNSC that was normal at Baseline (RW0; both values ≤ULN) and becomes abnormal (>ULN) based on each of two LNSC collections obtained on different nights

    AND

    In addition to one of the above partial-loss criteria, the subject must exhibit clinically significant worsening of signs and symptoms of CS, as determined by:

        - Clinically significant deterioration in disease-related signs or symptoms (using the signs and symptoms validated instrument

and/or physical examination).

OR

- Relevant deterioration in **one or more** disease-related biomarkers (see Table 3).

3. In the absence of loss or partial loss of cortisol response as defined above, clinically significant deterioration in disease-related signs or symptoms (using the signs and symptoms validated instrument and/or physical examination) **AND** clinically relevant deteriorations in **two or more** disease-related biomarkers (see Table 3).

The justification for early rescue must fall under one of the three scenarios above and must be described in the Case Report Form (CRF).

Table 3 Minimum Visit-to-Visit Serial Change in Biomarker that Could be Considered Potentially Relevant

	Reference Change Value (RCV)*	Source
Fasting Blood Glucose[1]	**17.9%** (e.g. an increase from 6.1 mmol/L to 7.2 mmol/L is an 18% change and meets the RCV threshold)	Santaguida 2005
Fasting Insulin[2]	**79%** (e.g. an increase from 173 pmol/L to 310 pmol/L is a 79% increase and meets the RCV threshold)	Borai 2013
Potassium	**10%** (e.g. a decrease from 4.0 to 3.6 mmol/L is a 10% change and meets the RCV threshold)	Turner 2012
Blood Leukocytes (WBCs)	**33.8%** (e.g. an increase from 7.0 to 9.4 x10^9/L is an increase of 34% and meets the RCV threshold)	Ricos 2004
Systolic/Diastolic blood pressure	Exceeds threshold for intervention[3]	

*The analyte reference change values (or intervention thresholds) are the **minimum** within-subject, between-visit (from RW0) change values that are to be considered potentially relevant for purposes of early rescue. A value exceeding the Reference Change Value (RCV) need not be considered clinically relevant, as such a change might not be predicted to be associated with clinical sequelae. Expert interpretation is therefore required beyond the minimum requirement.

4.4 Double-blind Restoration Phase

All subjects completing the Randomized Withdrawal Phase who do not meet early rescue criteria, will enter the 8-week Double-blind Restoration Phase, wherein they will continue to receive the randomly assigned blinded treatment regimen and in addition will receive blinded restoration study medication (placebo for those already receiving

[1] Glucose must be fasting for at least 12 hours

[2] Must be fasting for at least 12 hours. Biological variability in serum insulin reportedly depends upon the state of glucose tolerance. The RCV shown reflects an intermediate RCV, between the published RCVs for normal glucose tolerance and impaired glucose tolerance, i.e. equivalent to that for impaired fasting glucose. Subjects with impaired glucose tolerance (IGT) or diabetes may have higher expected variability in fasting serum insulin.

[3] Visit-to-visit variability is known to vary substantially between people, regardless of actual SBP or DBP. Therefore, a clinically relevant deterioration cannot be based on a single reference change value or other threshold that is applicable to all study subjects. Clinically relevant deterioration in mean SBP or DBP should be justified by exceeding an established intra-patient range of variability in blood pressure, ideally established with prior values from the current study or COR-2012-01.

levoketoconazole, or levoketoconazole for those receiving placebo), in order to restore all subjects to a Therapeutic Dose of levoketoconazole while concealing from subjects and study personnel the identity of study medications used during Randomized Withdrawal. If, in the opinion of the Investigator, an increased dose of study drug is required for subjects who are unable to restore their prior cortisol control (i.e. mUFC >ULN) during the Restoration Phase at their prior Therapeutic Dose, those subjects should be withdrawn from this study owing to "loss of efficacy". Such subjects may be considered for enrollment in the long-term OPTICS study or EAP if they otherwise qualify.

Subjects who complete all Randomized Withdrawal visits will undergo RW5 procedures immediately prior to administration of blinded Restoration Phase study medication (except ECG to be done 1-2 hours after administration of rescue medication). Subjects will return to the clinical site every 28 (± 5) days (i.e., between Visits RW5 and RES1 and between Visits RES1 and RES2) for safety and efficacy evaluations as indicated in the Time and Events Schedule (Appendix A). During the Restoration Phase starting at Visit RW5, approximately weekly contact will be made between visits (method unspecified) to inquire regarding AEs, subject status and to ensure compliance with study medication.

The titration with blinded restoration therapy will begin at RW5 with 1 tablet BID and will increase in 1 tablet increments every 2 days alternating AM and PM per Table 2 until the prior-established Therapeutic Dose regimen is matched unless the Therapeutic Dose is DL0. Thus, for illustration, a subject with a Therapeutic Dose of 300 mg BID (2 tablets BID) randomized to levoketoconazole during the Randomized Withdrawal Phase would rapidly titrate over 8 days to a total of 4 tablets BID during the Restoration Phase to include the addition of 2 tablets BID of placebo.

The reason for adding blinded study medication (as opposed to open-label) to the regimen during Restoration Phase is to maintain the blinded treatment assignment that occurred via randomization. This eliminates the risk of bias introduction from this knowledge.

RES2 procedures will also be performed by subjects who prematurely withdraw from the study during Restoration Phase.

5 SUBJECT SELECTION AND WITHDRAWAL CRITERIA

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

5.1 Inclusion Criteria for Specified Subjects Completing the SONICS Study

Subjects who have completed the SONICS study, within 6 months of the screening visit, including those receiving open-label treatment after SONICS as part of an EAP, may be eligible for the study if the following criteria are met:

1. Completed the final SONICS visit (M12) and have demonstrated maintenance of clinical response (partial or complete, as defined in the SONICS protocol, COR-2012-01) on a stable Therapeutic Dose of levoketoconazole for at least 12 weeks prior to study entry (i.e. Visit RW0).

2. Able and willing 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.

5.2 Inclusion Criteria for All Others:

The following categories of potential subjects, categorized by prior use of levoketoconazole, may be eligible if the following 11 inclusion criteria are all met:

- Naïve to levoketoconazole (defined as having never participated in SONICS);
- Completers of SONICS visit M12 more than 6 months of the screening visit of the current study;
- Completers of SONICS visit M12 within 6 months of the screening visit who have **not** been receiving a stable Therapeutic Dose of levoketoconazole for at least 12 weeks prior to the start of screening.

1. Male or female and at least 18 years of age.
2. Able and willing 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.
3. Confirmed newly diagnosed, persistent or recurrent endogenous CS of any etiology, except secondary to malignancy (including pituitary or adrenal carcinoma). Persistence will not be considered confirmed until 6 weeks or more post-surgery.
   The following historical evidence will be considered as sufficient to establish the cause of endogenous CS as being due to Cushing's Disease (CD) (i.e. ACTH-dependent of pituitary origin) specifically:

   - Pathological (e.g. ACTH-staining) or post-surgical confirmation of the diagnosis of CD (i.e. documented adrenal insufficiency post-adenomectomy or post-hypophysectomy) **OR**
   - Intermediate, normal or elevated plasma ACTH (i.e. at least 5 pg/mL [1.1 pmol/L]) **PLUS**

     <u>For tumors 6 mm and above by imaging:</u>

     a. Inferior petrosal sinus sampled (IPSS) ACTH central:plasma gradient at least 2 before corticotropin-releasing hormone (CRH) or at least 3 after CRH, OR in the absence of IPSS, either:

     b. Positive ACTH and/or cortisol response to CRH or desmopressin or combined CRH-desmopressin stimulation plus high-dose (8 mg) dexamethasone suppression of blood cortisol, ideally on more than one occasion OR

     c. Other adequate diagnostic testing. Such cases must be discussed with and explicitly approved by the Medical Monitor, and the specific diagnostic criteria used to establish the diagnosis of CD must be documented.

For tumors below 6 mm or not visible by Magnetic Resonance Imaging:

a. IPSS with ACTH central:plasma gradient at least 2 before CRH or at least 3 after CRH.
b. Other adequate diagnostic testing. In the absence of IPSS, an individual might be eligible if CD was otherwise confirmed via adequate testing. Such cases must be discussed with and explicitly approved by the Medical Monitor, and the specific diagnostic criteria used to establish the diagnosis of CD must be documented.

4. Elevated mean 24-hour UFC levels at least 1.5X ULN of the normative range of the study's central laboratory assay and from a minimum of three measurements from adequately collected urine; the study's central laboratory must be used for all qualifying measurements. **NOTE**: This criterion does not apply to subjects currently on levoketoconazole.
5. Presence of abnormal values from at least one of these two diagnostic tests: (discrepancies between test findings will not be investigated nor considered exclusionary)

   - Abnormal Dexamethasone Suppression Test (DST): Elevated 8 AM blood cortisol at least 1.8 μg/dL (50 nmol/L) after 1 mg dexamethasone orally at 11 PM the evening prior with concurrent dexamethasone blood concentration greater than 5.6 nmol/L (220 ng/dL) (results from within the 2 months prior to start of Screening or newly tested with results available by the Baseline Visit [TM0]). If the DST cortisol is elevated and the dexamethasone value is at least 3.9 nmol/L (153 ng/dL), then the subject could qualify if at least 1 LNSC is greater than the ULN of the study's central laboratory normative range (the study's test kit and lab must be used for all qualifying measurements), whereas a non-suppressed cortisol during DST with a dexamethasone value of at least 5.6 nmol/L (220 ng/dL) would be required if LNSC is not done or if both LNSC values are low (≤ ULN of the study's central laboratory normative range; the study's test kit and lab must be used for all qualifying measurements). OR
   - Elevated LNSC concentrations (at least two measurements) each greater than the ULN of the study's central laboratory normative range; the study's test kit and lab must be used for all qualifying measurements.

   NOTE: Abnormal LNSC is required among eligible subjects with estimated glomerular filtration rate (eGFR as determined by Modified Diet in Renal Disease [MDRD] equation) above 40 and below 60 mL/min/1.73 m^2.

   NOTE: This criterion does not apply to subjects currently on levoketoconazole.

6. Non-candidates for CS-specific surgery, refuse surgery or surgery will be delayed until after study completion and agree to complete this study prior to surgery.
7. If post-surgical for CS-specific surgery, then no significant post-operative sequelae remain and the risk of such sequelae is considered negligible.

8. Agree to the following minimum washout periods prior to the Baseline Visit (TM0) (as applicable):
    - 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.
9. Females who are either of non-child bearing potential (i.e. incapable of becoming pregnant), defined as:
    - Post-menopausal—age 50 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) OR
    - Surgically sterile—documented hysterectomy and/or bilateral oophorectomy or tubal ligation.

OR

    - Females of child-bearing potential who agree to use highly effective methods of birth control while participating and for 2 weeks after participation has completed (abstinence is considered acceptable if routinely practiced).
10. Men who, if fertile, agree to use an acceptable form of birth control, including abstinence if routinely practiced, while enrolled and for 2 weeks after participation has completed.
11. Able to comprehend and comply with all procedures.

5.3 Exclusion Criteria

Subjects will be excluded from the study if ANY of the following criteria are met (NOTE: exclusion criteria apply to and must be assessd in both cohorts):

1. Enrolled in SONICS but have not completed SONICS through Visit M12.
2. Pseudo-Cushing's syndrome based on assessment of the Investigator (for details see Appendix G).
3. Cyclic Cushing's syndrome with multi-week periods of apparent spontaneous CS remission.
4. Non-endogenous source of hypercortisolism, including pharmacological corticosteroids or ACTH.

5. Radiotherapy of any modality directed against the source of hypercortisolism within the last 5 years.
6. Treatment with mitotane within 6 months of 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. Clinical or radiological signs of compression of the optic chiasm.
9. Major surgery within 1 month of Screening (or within 6 weeks for pituitary surgery).
10. Clinically significant abnormality in 12-lead ECG during the Screening Phase requiring medical intervention (may be eligible once stable, to be determined case by case).
11. QTc interval above 470 msec during the Screening Phase via central reader interpretation.
12. History of Torsades des Pointes, ventricular tachycardia, ventricular fibrillation, history of prolonged QT syndrome (including first-degree family history).
13. Use of medications associated with possible, probable, or definite QT/QTc prolongation (unless subsequently washed out).
14. Pre-existing hepatic disease (except for mild to moderate non-alcoholic fatty liver disease documented by imaging or biopsy and with transaminase values within allowed limits).
15. Hepatitis B surface antigen (HbsAg) or hepatitis C-positive.
16. Human immunodeficiency virus (HIV)-positive.
17. History of symptomatic cholelithiasis with intact gallbladder.
18. History of pancreatitis.
19. Liver safety tests during the Screening Phase as follows:
    - ALT and/or AST above 3X ULN
    - AP or Total bilirubin above 2X ULN.

    Subjects with isolated indirect bilirubin up to 3X ULN are presumed to have Gilbert's syndrome and may be enrolled if all other liver safety tests are within normal levels.
20. History of documented or suspected drug-induced liver injury to ketoconazole or any other azole drug.
21. Serum potassium below 4.0 mEq/L (unless subsequently corrected and stable).
22. 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.

23. History of persistent, uncontrolled hypertension despite medical intervention.
24. Hypercholesterolemia currently treated with atorvastatin, lovastatin or simvastatin and unwilling or unable to change to alternative therapy with: pravastatin, fluvastatin, pitavastatin or rosuvastatin (must switch statin at least 2 weeks prior to dosing) or another allowed therapy. For subjects for whom lipid reduction therapy is being considered, all lipid lowering drugs should be added and stabilized for at least 4 weeks prior to TM0 for the levoketoconazole-naïve cohort or RW0 for the SONICS-completer cohort, as improvements in lipids are being assessed as an endpoint for levoketoconazole treatment in this study.
25. More than one hospitalization for hyperglycemia or complication of diabetes during the last 12 months
26. Decreased renal function as defined by eGFR below 40 mL/min/1.73 m^2, using MDRD equation for eGFR.
27. Pregnant or lactating.
28. Body habitus preventing repeated venipuncture as required by protocol.
29. Any other clinically significant medical condition, as determined by the Investigator that precludes enrollment and participation in the study through completion, including conditions that would preclude the subject from being able to follow instructions or perform necessary procedures (for example, psychiatric instability or severe disability).
30. History of alcohol or drug abuse in the 6-month period prior to Screening.
31. Currently participating in another study or has received any investigational treatment (drug, biological agent or device) other than levoketoconazole (COR-003), within prior 30 days or five half-lives of treatment, whichever is longer.
32. 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). A list of acceptable oral antacids will be provided; if used, antacids must be ingested at least 2 hours **after** dosing of levoketoconazole.
33. Current use of any prohibited concomitant medication that cannot be discontinued safely and washed out completely prior to the Baseline Visit (TM0 or RW0, for the levoketoconazole-naïve and SONICS-completer cohorts, respectively), including but not limited to the following (a more complete list is included in Appendix J):

    - 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 rice yeast, danshen, silybum marianum, Asian ginseng, schissandra sphenanther, shankhapushi, and Asian herb mixture (Xiao chai hu tang and Salboku-to);
- Topical or inhaled corticosteroids;
- Carbamazepine, fenofibrate, carbenoxolone;
- Drugs that pose unacceptable risk due to overlapping or exaggerated toxicities or pharmacological action due to presumed PK or pharmacodynamic interactions with levoketoconazole;
- Genuine licorice.

5.4 Withdrawal Criteria

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;
- Safety reasons, as stipulated in Sections 5.4.1, 5.4.2, and 5.4.3 either at the discretion of the Investigator or at the subject's request (see also Section 4.2.2.3.4);
- Protocol violations at the discretion of the Sponsor;
- Concomitant therapy that could interfere with the results of the study (the Investigator will report all such information on the CRFs and decide, in accordance with the Sponsor, whether the subject is to be withdrawn);
- Failure to achieve the Therapeutic Dose during the TM Phase;
- Closure of randomization while still in the TM Phase.

All study withdrawals and their causes must be carefully documented by the Investigator on the CRF, and, if need be, on the AE page. The reason for withdrawal will be entered in the CRF. All data gathered prior to withdrawal will be made available to the Sponsor. All withdrawn subjects will be asked to report to the clinic to complete the assessments at the end of the relevant study phase at either Visit TM7 or RW5 or RES2, as appropriate (see Appendix A). All AEs will be followed until resolution or at least 30 days after the last dose of study medication.

Consult Section 11.2 for study additional withdrawal procedures.

Consideration of study withdrawals due specifically to QTc interval prolongation or suspected or confirmed liver injury are described in Sections 5.4.1 and 5.4.2, respectively.

5.4.1 Withdrawal due QTc Interval Prolongation

See Section 6.4.3.1 for guidance on the assessment of QTc interval prolongation, including gathering evidence of persistence and confirmation of causal relationship to study medication.

Persistent, Confirmed as Related QTc Prolongation During Titration and Maintenance Phase

If persistent and confirmed levoketoconazole-related QTc interval prolongation greater than 500 msec or increase from Baseline (TM0) more than 60 msec is identified, an attempt may be made to manage it by temporarily holding the dose or dose reduction, as described in Section 6.4.3.1. However, if such prolongation is observed at the lowest levoketoconazole dose (150 mg/day), administration of the study drug must cease permanently and the subject must be withdrawn. In all cases, a PK sample should be collected as close to the time of the event as possible.

Persistent, Confirmed QTc Prolongation During Randomized Withdrawal Phase or Restoration Phase

QTc prolongation is unexpected during these phases owing to prior establishment of the Therapeutic Dose. However, in the event of a persistent confirmed as related, QTc prolongation greater than 500 msec or increase from Baseline (RW0) more than 60 msec is identified, blinded study medication should be temporarily held, electrolytes and other correctable confounding factors addressed, and QTc re-checked within 2 to 4 days. Consideration should also be given to cardiology referral if the prolongation is considered clinically urgent.

If QTc interval prolongation does not respond to temporary blinded study medication stoppage or recurs after restarting study medication, the subject should stop study medication permanently and withdraw from the study. If the QTc interval returns to a normal value and remains normal, the subject may continue in the study per the usual visit schedule, with interim QTc interval checks added for monitoring purposes.

5.4.2 Withdrawal due to Suspected or Confirmed Drug-induced Liver Injury

Although newly recognized liver abnormalities will be less likely for subjects who have completed the SONICS study than for levoketoconazole-naïve subjects, both cohorts will be monitored in the same way for liver abnormalities during the Randomized Withdrawal Phase and the Restoration Phase. Study withdrawal due to abnormal liver-safety tests will likewise be prompted using the same criteria and evaluation procedures, as described below. See Section 4.2.2.3 for details describing management of suspected liver injury other than study withdrawal.

Recommendations from the FDA Guidance on Drug-Induced Liver Injury: Premarketing Clinical Evaluation (May 2009) have been adopted for use in this study to monitor for evidence of early liver injury. Per the FDA guidance, discontinuation of investigational therapy should be considered in the case of:

- 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** total bilirubin above 2X ULN or International Normalized Ratio (INR) above 1.5 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
- 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 total bilirubin above 2X ULN in the absence of evidence for obstruction or Gilbert syndrome. NOTE: An ultrasound evaluation of the gallbladder and bile duct should be conducted to exclude cholestasis as the cause for elevated AP and/or total bilirubin.
- Not included in FDA guidance but additionally specified for this study as a finding that should prompt evaluation and possible action: Subjects with ALT or AST above 3X ULN or AP above 2X ULN (in the absence of evidence for cholestasis) or total bilirubin above 2X ULN (in the absence of evidence for cholestasis and except for subjects enrolled with presumed Gilbert's syndrome)

Guidelines for dose interruption, follow-up and rechallenge with study medication in cases meeting the above criteria are found in Section 4.2.2.3.

Upon reporting liver-safety lab test observations as AESIs, the Sponsor will provide Investigators with suggested evaluation procedures to determine the etiology of the abnormalities as outlined in Appendix O. While liver safety tests 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. In all cases, a PK sample should be collected as close to the time of the event as possible.

Withdrawal from Study

Prior to considering study withdrawal, but after interrupting use of study medication, subjects meeting the above criteria at any visit should be evaluated with serial (repeated) liver safety test and INR evaluations and potentially additional diagnostic evaluative testing to establish an etiology of the abnormalities so that the etiology might be determined definitively while the subject remains available for evaluation.

If liver safety test abnormalities persist for more than 4 weeks following interruption of study medication or demonstrate a trend of worsening following interruption, then the subject should remain off study medication permanently and be withdrawn from the study. The subject will continue to be followed post-withdrawal until resolution or near-normalization of the laboratory abnormality that resulted in the premature study withdrawal. The withdrawn subject will not be eligible to enroll in either the OPTICS study or the EAP program.

5.4.3 Withdrawal due to Adrenal Insufficiency

Guidelines for dose interruption, follow-up and rechallenge with study medication in cases meeting the above criteria are found in Section 4.2.2.3.

If adrenal insufficiency is suspected and the subject is taking the lowest levoketoconazole 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. In all cases, a PK sample should be collected as close to the time of the event as possible.

6 STUDY ASSESSMENTS AND PROCEDURES

There are two cohorts of subjects potentially eligible (SONICS-completer and levoketoconazole-naïve); study methodology varies by cohort only prior to randomization as outlined in Section 6.1 (SONICS-completer cohort) and Section 6.2 (levoketoconazole-naïve cohort).

The Baseline visit for purposes of the primary efficacy endpoint for both cohorts is the first visit in the Double-blind Randomized Withdrawal Phase (RW0). **RW0 may coincide temporally with Visit M12 (in SONICS), or RW0 may occur after this visit, depending on the specific circumstances of the subject.**

For purposes of comparing findings from post-Baseline safety assessments to Baseline findings, TM0 should be used as the Baseline if the change or finding occurs during the TM Phase; otherwise RW0 will serve as the Baseline. For purposes of comparing the QTc interval to Baseline for determining if an AESI is has occurred the shorter QTc interval from the two baselines (TM0 and RW0) will serve as the QTc Baseline. Refer to Section 13.2.2 for information regarding the assessment of QTc prolongation for determining AESIs.

All subjects must meet eligibility criteria prior to randomization. A screen failure occurs when a signed informed consent has been obtained, but the subject fails to meet some or all eligibility criteria at the Baseline visit (Visit RW0 for the SONICS-completer cohort or, Visit TM0 for the levoketoconazole-naïve cohort.

The exact timings of each assessment are provided in the Time and Events Schedules (Appendix A). Detailed procedures are provided in the SPM. The study is being conducted as described in Appendix C and reported in accordance with the guidelines presented in Appendix D and Appendix E. Any changes to the study design are managed in accordance with Appendix F.

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 local standard of care. Changes to a subject's medical condition or concomitant therapies resulting from such interventions, must be documented in the CRF as an unscheduled visit.

6.1 SONICS-completer Cohort

For the SONICS-completer cohort, the study will consist of the following Phases with approximate timings:

- A Screening Phase (of approximately 2 weeks' duration)
- Double-blind Randomized Withdrawal Phase (approximately 8 weeks' total duration, maximum 9½ weeks)
- Double-blind Restoration Phase (approximately 8 weeks' total duration, maximum 9½ weeks)

After signing the informed consent, subjects will attend the Screening/Baseline visit to check eligibility and, if eligible, proceed to be randomized and complete Baseline procedures as detailed in the Time and Events Schedules (Appendix A). Visit RW0 may occur concurrently with SONICS Visit M12 or afterward, depending on the time when the subject exited SONICS and the availability of UFC data to confirm that UFC response has been maintained. Data from the SONICS study and assessments that overlap may be utilized for this study for purposes of determining eligibility and establishing Baseline values (e.g. data from vital signs may be recorded in the eCRF for both studies.

NOTE: The duration between exiting SONICS and enrolling in the current study may in unusual cases be more than 6 months. In such cases, subjects must undergo the same Screening procedures as levoketoconazole-naïve cohort to confirm eligibility. However, such subjects will NOT have to dose-titrate if they have been receiving levoketoconazole therapy at their stable Therapeutic Dose throughout the 12 weeks immediately prior to Screening.

6.2 Levoketoconazole-naïve Cohort

For the levoketoconazole-naïve cohort, the study will consist of the following Phases with approximate timings:

- Screening Phase (approximately 13 weeks' duration to allow for prior medication washout; there is no required minimum Screening interval).
- Dose Titration and Maintenance Phase (not less than 14 weeks in total and for no more than approximately up to 19 weeks' total duration). In exceptional situations, subjects may require additional time (i.e. greater than 19 weeks) to achieve the Therapeutic Dose. These situations must be approved on a case by case basis by the Medical Monitor.
- Double-blind Randomized Withdrawal Phase (approximately 8 weeks' total duration, maximum 9½ weeks).
- Double-blind Restoration Phase (approximately 8 weeks' total duration, maximum 9½ weeks).

After signing written informed consent, subjects will enter the Screening Phase. After performing the initial Screening assessments, subjects on previous CS therapies or other prohibited therapies must enter a washout period, as applicable (see Section 4.2.2) before

completing all Screening assessments detailed in the Time and Events Schedules (Appendix A).

Baseline evaluations for the TM Phase will be obtained as part of the Screening assessments and should be conducted AFTER completion of all initial Screening procedures and after subjects have undergone a sufficient washout period from previous CS therapies (see Section 5.2), if applicable. Collections of LNSC and UFC obtained during Screening will provide the Baseline measurements if collected within 14 days of receiving first dose of levoketoconazole. NOTE: all Baseline UFC and LNSC values must be obtained after washout of any medications (except levoketoconazole) that are known to influence cortisol. LNSC results that are unavailable from Screening within 2 weeks of dosing should be re-collected prior to dosing at TM0. Results from the Baseline assessments are necessary to determine if the subject remains eligible for participation in the TM Phase of the study.

Visit TM0 is the Baseline visit for the TM Phase of the study for purposes of establishing QTc interval and safety laboratory Baseline values, as well as certain secondary efficacy endpoint values. TM0 is **not** the Baseline for purposes of the primary efficacy endpoint. RW0 is the Baseline for purposes of the primary endpoint.

At the end of the TM Phase, subjects will attend the randomization Baseline visit (RW0) to check eligibility and, if eligible, proceed to be randomized and complete Baseline procedures as detailed in the Time and Events Schedules (Appendix A). Visit RW0 may occur concurrently with TM7 or no more than 11 (+3) days later unless a dose change is required at TM7.

6.3 Demographic/Medical History Assessments

NOTE: Subjects who have recently completed the SONICS study (within 6 months of Screening) will undergo demographic and medical history assessments to confirm eligibility. Historical information from all SONICS visits will be used for this purpose and captured in the current study database, including ECG, imaging and laboratory data. While subjects who have distantly completed the SONICS study (i.e. more than 6 months since completing Visit M12) will also have historical SONICS data available for use and import into the current study database, they must also have a complete Screening assessment with updated testing, the same as the levoketoconazole-naïve cohort.

The following demographic characteristics will be captured at Screening:

- Date of birth;
- Gender;
- Race and ethnicity.

Medical and medication history will be assessed and collected as related to the Eligibility Criteria in Section 5), and will include but not be limited to the following:

- Documentation of diagnosis of CS, including but not limited to evaluations for CS during the previous 6 months.
- Documentation of current CS co-morbidities.

- Documentation of prior management of CS during the previous 6 months, including medications, diagnostic tests (including imaging), surgical or radiation therapies.
- Documentation of clinical laboratory data from the previous 3 months, if available; specifically: liver safety tests (ALT, AST, AP, LDH, direct and total bilirubin), HbA1c, fasting serum glucose and glucose following an oral glucose tolerance test (OGTT), serum lipid panel (LDL-C, HDL-C, total cholesterol, triglycerides), hsCRP, urinary albumin/creatinine ratio, and testosterone concentration.
- Documentation of blood pressure data for the previous 3 months, if available.
- Medication history during the previous 3 months, asking specifically about blood pressure, anti-diabetic, cholesterol lowering and anti-inflammatory drugs.
- Drug and alcohol use.

6.4 Safety and Efficacy Assessments

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

Full physical examinations will be performed by a study physician at the times indicated in the Time and Events Schedules (Appendix A). The physical examinations will be inclusive of all body systems, except that genitourinary and rectal examinations may be waived at the discretion of the Investigator, and should include height (cm) and weight (kg). Abdominal girth (cm) will be measured in triplicate and body habitus will be assessed at the times indicated in the Time and Events Schedule and as described in the SPM. Body mass index (BMI) will be calculated based on data entered in the CRF during that visit.

The examining physician or a qualified HHC professional with training will be asked to complete a questionnaire related to the assessment of Clinical Signs and Symptoms of CS (see Appendix M). The person completing the Signs and Symptoms of Cushing's assessments should, when possible, remain consistent for individual subjects. The results will be used to quantify changes in Clinical Signs and Symptoms of CS. In cases of clinically significant deterioration of clinical signs and symptoms of CS, HHC professionals should refer the subject back to the physician for corroboration prior to initiation of early rescue therapy.

6.4.2 Vital Signs

Vital sign measurements will include temperature, sitting systolic blood pressure (SBP), sitting diastolic blood pressure (DBP) and heart rate (HR) at Baseline and at each visit throughout the study (see Time and Events Schedules in Appendix A).

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.
- Blood pressure measurements will be made in triplicate, at least 3 minutes apart, over approximately 10 minutes, after the subject has rested in a sitting position for at least 10 minutes.

Heart rate will also be recorded in triplicate, also approximately 3 minutes between each assessment. The three measurements for heart rate and blood pressure will each be recorded individually in the CRF and a mean value for heart rate and blood pressure 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 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 I.

6.4.3 12-Lead Electrocardiograms (ECG)

Male patients with CS have been reported to have prolongation of the QT interval [Giraldi 2011]. Thus, inclusion criteria have allowed for this possibility; both males and females with mild QTc prolongation will be allowed into the study if Baseline QTc is not greater than 470 msec. The potential risk of protracted prolongation of the QTc interval is the development of an arrhythmia called Torsade de Pointes. The development of Torsade de Pointes in the face of QTc interval prolongation is rare, and appears to occur primarily when the QTc interval is particularly prolonged and generally longer than 500 msec or more than 60 msec above Baseline.

Therefore, subjects with prolonged QTc intervals above 500 msec or above 60 msec increase over the QTc interval at the Screening or Baseline visit must not receive study medication until the QTc has returned to a value no more than 500 msec or no more than 60 msec change from Baseline. For purposes of comparing the QTc interval to Baseline, TM0 should be used as the Baseline value if the QTc prolongation occurs during the TM Phase; otherwise RW0 will serve as the QTc Baseline. If the QTc does not shorten sufficiently and stably, the subject will be ineligible for dosing. Note that QTc interval is highly variable during the day, and food intake can transiently shorten QTc interval. Nausea, vomiting, upset stomach, dizziness and electrolyte abnormalities (including hypokalemia/hypomagnesemia) can also cause prolongation in the QTc interval. Such factors should be considered and avoided during QTc measurements.

Many drugs can prolong the QTc interval directly or indirectly through interference with the metabolism of QT-prolonging drugs. Levoketoconazole appears to have the potential to prolong QTc both directly and indirectly.

In this study, ECG monitoring is being performed at the designated times (see Time and Events Schedules 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 by a cardiologist employed 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 locally and transmitted to Spaulding for central reading via printout.

The following procedures will apply to all ECG recordings:

- ECGs will be obtained within approximately 1 to 2 hours after drug administration (i.e., at approximately Tmax of levoketoconazole)
- No food should be consumed for a total of at least 2 hours prior to ECG acquisition, unless necessary to avoid hypoglycemia or to relieve nausea. Food intake must be recorded in the CRF.
- ECGs will be obtained after the subject has rested in a supine position for at least 5 minutes.

6.4.3.1 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 J). 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 potassium, magnesium and calcium concentrations and for PK (levoketoconazole concentration) evaluation.
  - 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.
  - If electrolytes are normal and no other cause can be identified to account for the absolute QTc interval above 500 msec (or above 60 msec above Baseline), 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, must be recorded in the CRF.
- Whenever persistent and confirmed QTc prolongation is observed (defined below), an additional PK sample should be collected as close to the time of the event as possible.

<u>Persistent, confirmed QTc prolongation</u>

Persistent and confirmation of QTc prolongation is defined as follows:

- Persistence: An ECG repeated (ideally) within 30 minutes of the first ECG that also reveals QTc prolongation.
- Confirmation: The Investigator should consider alternative possibilities as causative or contributory to the QTc prolongation as described above. Once alternative

possibilities are ruled out and persistence is documented by automated interpretation, QTc prolongation may be considered as preliminarily confirmed for safety reporting and immediate-intervention purposes. Final confirmation of QTc prolongation, however, will be based on the Spaulding cardiologist over-read of the integrated ECG. Final confirmation data will be used to summarize QTc findings.

Regardless of seriousness or causality, instances of persistent, preliminarily or definitively confirmed QTc prolongation should be reported to the Sponsor's designated Pharmacovigilance group as an AESI within 24 hours from the time the persistence has been preliminarily confirmed, similar to the reporting for SAEs (see Section 13.7).

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

If the subject is on the lowest possible dose of study medication (150 mg/day) in the TM Phase and has persistent and presumed study medication-related QTc interval prolongation of more than 500 msec or a change from Baseline longer than 60 msec, administration of the study drug will cease permanently and the subject will be withdrawn. See also Section 5.4.1 for withdrawal criteria for persistent, confirmed QTc prolongation.

During any other phase of the study, or if the subject is receiving doses greater than 150 mg/day in the TM Phase, persistent and presumed study medication-related QTc changes may be managed by temporarily withholding study medication. Subsequently, if a confounding etiology is eventually identified, study medication may be restarted.

During the TM Phase, 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 for increased safety monitoring.

In all other study phases, temporarily withheld study medication for QTc prolongation may, in some cases, be resumed, using the same regimen, after confirmed QTc correction. However, unless an etiology other than study drug has been implicated, QTc prolongation will usually result in permanent study medication discontinuation and study withdrawal (see Sections 5.4.1 and 6.4.3.1).

Additional information for evaluating and managing prolonged QTc Interval is available in Appendix O.

6.4.4 Clinical Laboratory Tests

Samples for clinical laboratory testing will be collected at the times indicated in the Time and Events Schedules (Appendix A). A complete list of all the analytes is provided in Appendix B. In addition to routine chemistry, hematology and urinalysis, laboratory analytes will include: serum cortisol, ACTH, TSH, FT4, prolactin, free and total testosterone, coagulation measures (prothrombin time [PT], partial thromboplastin time [PTT], INR), triglycerides, lipid panel (total cholesterol, LDL-C, HDL-C, LDL-c:HDL-C ratio), fasting insulin for calculation of HOMA-IR, HbA1c, hsCRP, and spot urine for

albumin/creatinine ratio to determine microalbuminuria. Also, in women only: FSH estradiol, and urine pregnancy test. Screening safety laboratory tests will also include the following: HIV and antibodies against hepatitis B and C. All scheduled testing will be conducted in the fasted state and in the morning unless stated differently in the Time and Events Schedules (Appendix A).

Liver safety monitoring including AST, ALT, total bilirubin, LDH, GGT and AP, will be performed throughout the study. In addition, liver safety tests should be measured immediately if a subject develops 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, medical evaluation of such symptoms must also include assessment of liver safety tests.**

6.4.4.1 Prevention of Pregnancy

Regardless of menopausal status, all female participants must have a negative pregnancy test at study visits indicated in the Time and Events Schedules (Appendix A). Urine beta human chorionic gonadotropin (βhCG) will be assayed on site; results of the test must be available before dosing can begin (levoketoconazole-naïve cohort) or before randomization (SONICS-completer cohort).

Post-menopausal is defined as age greater than 50 with amenorrhea for at least 12 consecutive months, accompanied by elevated FSH (at least 23 mIU/mL) and low estradiol (no more than 40 pg/mL [140 pmol/L]) during the Screening Phase (Appendix B).

Women of child-bearing potential must agree to use an effective form of contraception for up to 2 weeks after study completion. 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 levonorgestrel 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 (IUD); 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.

Fertile men must agree to use a double-barrier method of contraception (condom plus spermicide or diaphragm plus spermicide) or abstinence, if routinely practiced, while participating in the study and for 2 weeks after the last dose of study drug OR, the male subject or his female partner must be surgically sterile (e.g. vasectomy, tubal ligation) or the female partner must be post-menopausal.

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.

6.4.4.2 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 Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor 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 Sponsor. However, Investigators are not obligated to seek such information proactively from former study participants.

6.4.5 Disease-Related Assessments

6.4.5.1 24-Hour Urinary Collections for Free Cortisol (UFC)

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

Please see the SPM for details on urine collection procedures. Note that, in addition to following the lifestyle and dietary restrictions listed in Section 7, 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 the containers provided. Subjects will be asked to provide either **two** or **three** adequate 24-hour urine collections, collected over sequential days per the times indicated in the Time and Events Schedules (Appendix A) prior to the actual scheduled visit during the TM phase, as results are needed to determine if dose escalation is required, or whether a confirmatory UFC is needed to establish Therapeutic Dose. If subjects immediately roll-over at SONICS M12, the two UFC samples collected for that

visit can be used (if within 6 weeks of the baseline visit) and one additional confirmatory sample will need to be collected for LOGICS screening (after the informed consent form for LOGICS has been signed). 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 may be repeated at the discretion of the Investigator and/or the Sponsor; the rationale for repeat collections should be captured in the CRFs.

Important: Subjects **must** continue to be seen in clinic no less than approximately once every 2 weeks during the TM Phase and no less than approximately once every 4 weeks during Randomized-Withdrawal, even if the need for repeated 24-hour urine collections delays progress to a subsequent study phase. The time spent repeating inadequately collected 24-hour urine specimens must be actively managed by the Investigator to minimize delays in progressing a subject through the study as per the Time and Events Schedules (Appendix A).

For the levoketoconazole-naïve cohort, 24-hour urine collections for assay of UFC are required at Screening and throughout the TM Phase as follows:

- At Screening and the last visit in the TM Phase (TM7) if applicable, subjects will be asked to provide a total of **three** adequate 24-hour urine collections.
- During the TM Phase, after progressing to a new dose level, subjects will be asked to provide **two** 24-hour urine specimens to assess the need for further dose titration. The first 24-hour urine collection will be on Day 8 (±2 days), relative to starting the dose level (i.e. Day 1), and the second collection will be on Day 9 (±2 days). Subjects will be asked to transport or, preferably, ship via the provided courier service, their urine collections to the clinic, as soon as possible after collection ends (ideally on or before Day 10). Urine volume will be measured at the clinic (or by HHC professional) prior to shipping to the central laboratory. Aliquots of collected samples will be shipped frozen to the designated central laboratory for measurement of UFC as soon as possible after receipt to allow rapid turnaround of results to facilitate decision-making.

  Section 4.2.2.2.1 includes additional details of the dose titration process and determination of the Therapeutic Dose. As part of this process, an additional adequate 24-hour urine collection will be obtained to confirm if a Therapeutic Dose has been reached. As described above three adequate 24-hour urine collections will also be obtained routinely just prior to the last visit in the TM Phase (TM7).

For all subjects who enter the Double-blind Randomized Withdrawal Phase and Restoration Phase, either 2 or 3 24-hour urine collections are required, depending on the visit, as described in Table 9. For the urine collection between RW5 and RES1, subjects should have received the previously achieved Therapeutic Dose of blinded study medication for at least 1 week before collections commence and complete and at least 1 week before the RES1 visit. For urine collections between RES1 and RES2, urine collection should commence at approximately Day 18 of the Restoration Phase.

Urine collections will begin after the first morning void (collection Day 1) and will be collected over 24 hours until the next morning, including the first void on the morning of collection Day 2. **Careful instructions must be provided to the subject on the process for proper urine collection and cold-storage of samples over 24 hours. All supplies 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 up to age 70 years are provided in Table 4.

Table 4 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 ranges 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 lower end of the ranges reported in Table 4 [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 urine collection.

Urinary Sample Analysis

UFC levels from the 24-hour urine collection will be assayed at a central laboratory as per validated methodology using high pressure liquid chromatography tandem mass spectroscopy (HPLC/MS/MS).

6.4.5.2 Collection of Late-Night Salivary Samples for Free Cortisol (LNSC)

Late night salivary samples will be collected by each subject at the times indicated in the Time and Events Schedules (Appendix A) for LNSC determination prior to the actual scheduled visit. If subjects immediately roll-over at SONICS M12, one LNSC sample collected for that visit can be used (if within 2 weeks of baseline visit) and one additional confirmatory sample will need to be collected for LOGICS screening (after the informed consent form for LOGICS has been signed). Saliva collections must be done between

11 PM and midnight and following the lifestyle and dietary restrictions listed in Section 7. Subjects should not sleep and subsequently awaken within 2 hours before collecting the saliva sample.

For the levoketoconazole-naïve cohort, late night samples from 2 nights are required at Screening and throughout the TM Phase as follows:

- Late night samples from 2 nights, will be collected at Screening within 2 weeks of Visit TM0 and at the end of the TM Phase (Visit TM7). LNSC that is unavailable from Screening within 14 days of scheduled dosing at Visit TM0 should be recollected prior to dosing at TM0 (Appendix A).

For all subjects who enter the Double-blind Randomized Withdrawal Phase and Restoration Phase, late night salivary samples from 2 nights are required as follows:

- Late night samples from two nights, will be collected at the beginning (Baseline; Visit RW0), at the end (Visit RW5) of the Randomized Withdrawal Phase, and at the end of the Restoration Phase (RES2).

Late-night salivary samples from a single night's collection will be collected at the times indicated in the Time and Events Schedules (Appendix A). All samples will be analyzed at a central laboratory. Details for collection and handling of samples are provided in the SPM and laboratory manual.

6.4.5.3 Dexamethasone Suppression Test (DST) (levoketoconazole-naïve cohort)

An overnight DST (1-mg test as described below) will be performed during Screening if not previously performed within 2 months (up to 60 days) prior to the start of Screening Phase, to confirm eligibility for participation in the study. The DST test is not needed at screening for subjects currently receiving levoketoconazole at the time of the Screening visit. This test can be completed as a home visit during the Screening Phase. To be considered adequate for this study, the procedure described below must be used.

Overnight 1-mg DST

- A 1-mg dose of dexamethasone will be administered orally between 11 PM and midnight;
- A blood sample to measure serum cortisol **and another** to measure dexamethasone must be obtained at approximately 8 AM the next morning; the exact time of collection must be recorded in the CRF;
- Subjects will have nothing to drink or eat, except sips of water, for at least 10 hours before blood is taken.

NOTE: If an LNSC sample is collected on the same night that dexamethasone is administered, the LNSC sample should be taken **prior to** dexamethasone administration. Because of the prolonged biological half-life of dexamethasone, to minimize the duration of Screening, UFC and LNSC samples should ideally be collected just prior to dosing with dexamethasone (as an example LNSC can be collected at 11:00 pm on the night of

the day when the last UFC sample collection was complete and this could be followed by dosing with dexamethasone at 11:30 pm). If collecting these samples after administering dexamethasone, do not collect LNSC until at least 5 days after dexamethasone is administered; do not collect UFC until at least 14 days after dexamethasone is administered.

Medications that induce CYP3A4 activity or otherwise interfere with the assay of cortisol may affect DST results. Example include: barbiturates, corticosteroids, phenytoin, rifampin, and tetracyclines.

6.4.5.4 Morning Cortisol and Adrenocorticotrophic Hormone (ACTH)

Morning serum cortisol (untimed) and ACTH levels will be measured in all subjects as described in the Time and Events Schedules in Appendix A.

6.4.5.5 Pituitary Magnetic Resonance Imaging (MRI)

Pituitary MRIs are not limited to subjects with a history of pituitary adenoma (e.g. CD), as this study will also assess the effects of levoketoconazole on pituitary size in subjects with ectopic ACTH or adrenal CS. Pituitary MRIs will be obtained for subjects who are levoketoconazole-naïve or completed SONICS more than 6 months prior to screening, if not previously done within 6 months of TM0 or RW0. For subjects who have recently completed SONICS, the SONICS M12 MRI may be used. If a pituitary MRI is not available, then results of a CT scan may be recorded.

Pituitary MRIs will also be obtained for all subjects who enter the study at Randomized Withdrawal Phase (RW0) [the SONICS visit M12 MRI may be used for subjects who completed the SONICS Study within 6 months] and again at Visit RW5. The Visit RW0 and RW5 MRI may be performed up to 2 weeks BEFORE the visit. The results of MRIs obtained during the study will be evaluated by a central reader (neuroradiologist) and pituitary size determined, including measurement of tumor if one is visible.

6.4.5.6 Oral Glucose Tolerance Test (pre-diabetic subjects with IFG only)

All pre-diabetic subjects (and only prediabetic subjects) with Baseline fasting glucose concentrations at least 100 mg/dL (5.6 mmol/L) but below 126 mg/dL (7.0 mmol/L) (i.e. with IFG) and who are not receiving medications to lower blood glucose (i.e. antihyperglycemics) will have an OGTT at the times indicated in the Time and Events Schedules (Appendix A). Subjects with diabetes, as defined in Appendix H will be excluded from the OGTT.

After an overnight fast of at least 12 hours, subjects will be asked to drink 75 g of glucose. Blood samples for the determination of glucose and insulin will be drawn before glucose administration and 30, 60, 90, and 120 minutes after administration.

6.4.5.7 Quality of Life and Psychometric Assessments

The Cushing QoL questionnaire (Webb 2008) (Appendix L) and the Beck Depression Inventory (BDI-II) (Appendix N) instrument will be administered at the times indicated in the Time and Events Schedules (Appendix A).

6.4.6 Situations Requiring Additional Safety Monitoring

Additional safety monitoring will be required for the following situations. This list is not intended to be an all-inclusive list of situations that could prompt additional safety monitoring.

6.4.6.1 Dose Titration Levels 750 mg/day or Above

If titration levels are 750 mg/day or above, subjects are required to return to the clinic or be seen at home by a qualified HHC professional for one extra safety evaluation 5 days (± 2 days) after each dose level escalation. Additional safety evaluations will include the following assessments: AEs, vital signs, routine safety laboratory assessments (liver safety tests), ECGs, and morning serum cortisol levels (see Section 4.2.2.4).

6.4.6.2 QTc Prolongation

In the event QTc prolongation occurs (as defined in Section 6.4.3.1), additional safety monitoring is required, including medical observation of the subject until the QTc interval has returned to a value no more than 500 msec or no more than 60 msec change from Baseline. Additional evaluation of the subject, as described in Section 6.4.3.1 and Appendix O, will include the potential requirement for additional ECGs, laboratory assessments and PK samples. Cases of persistent, confirmed QTc prolongation should be reported to Chiltern Pharmacovigilance as AESIs (Section 13.7).

6.4.6.3 Adrenal Insufficiency

Subjects with suspected adrenal insufficiency should be assessed for signs and symptoms of adrenal insufficiency and cortisol levels as described in Section 6.5.3 and Appendix O. Should mild adrenal insufficiency be deemed present, study drug should be temporarily discontinued. For moderate or severe symptoms/signs, study drug will be temporarily discontinued and rescue glucocorticoids administered as indicated. In all cases, a PK sample should be collected as close to the time of the event as possible.

Study drug at an appropriately lower dose can be restarted once the medical situation is deemed sufficiently resolved by the Investigator. When adrenal insufficiency is observed at DL1, subjects may be provided a lower dose of **150 mg QD (DL0)** following agreement with the Sponsor. Subjects may resume the Dose Titration scheme after a dose reduction at the discretion of the Investigator and agreement of the Sponsor. Cases of suspected adrenal insufficiency should be reported to Chiltern Pharmacovigilance as AESIs (Section 13.7).

6.4.6.4 Liver Function Test Abnormalities

Subjects with abnormal liver safety tests as described in Section5.4.1 will be monitored more intensively if they meet the criteria described. Such monitoring consists of repeating the usual liver test battery and might include additional evaluations to evaluate the etiology of the suspected liver injury. Guidance regarding temporary dose interruption and rechallenge is found in Section 4.2.2.3 Cases of possible drug-induced liver injury should be reported to Chiltern Pharmacovigilance as AESIs (Section 13.7). The Sponsor will provide suggested diagnostic tests in cases that are reported as AESIs

(Appendix O). In all cases, a PK sample should be collected as close to the time of the event as possible.

6.4.7 Pharmacokinetics

6.4.7.1 Pharmacokinetics Sample Collection

Blood samples (1 mL minimum) for the determination of plasma concentrations of levoketoconazole during a PK visit will be obtained at the following times relative to dosing during the study visit per the Time and Events Schedules (Appendix A).

During the TM Phase, PK samples should be drawn pre-dose and between 1.5 to 2.5 hours after dosing (i.e. at estimated Tmax) at TM0 and TM7 and at approximately 6-8 hours after dosing at one interim visit (TM2-TM6 or an additional safety visit) of the subject's choosing. The 6-8-hour time point for PK sampling is not optional. PK sampling at TM3, TM4, TM5, and TM6 could alternately be performed during additional safety visits required for DL4, DL5, DL6 and DL7 if those dose levels are needed.

During the Restoration Phase, PK samples should be drawn pre-dose and between 1.5 to 2.5 hours after dosing only at RES1.

Subjects will be asked to provide the time of the last dose on the day prior to the PK sampling visit and to forego taking study medication on the day of the scheduled visit, so that **dosing can be done at the clinic**.

Actual dosing and PK sampling times can vary from nominal (i.e. ideal or scheduled) times. The following time deviation windows will be allowed for collection of PK samples:

Sample timepoint	Allowed window (minutes)
Predose	30 minutes
1.5 to 2.5 hours	10 minutes
6 to 8 hours	30 minutes

For purposes of data entry, the actual dose administered, the actual time of drug administration, and the actual times of PK sample collection should be recorded rather than nominal times.

Additional PK sampling

To explore relationships between certain AEs (AESIs) and plasma exposure to drug, additional PK sampling is requested in the following situations:

If persistent and confirmed QTc prolongation is observed, an additional PK sample should be collected as close to the time of the event as possible, ideally within 1 to 2 hours of dosing (see Section 6.4.3).

PK samples should also be collected in association with other AESIs, i.e. liver test abnormalities considered possibly related to drug and suspected adrenal insufficiency, as close to the time of the event as possible (Section 13.2.2).

6.4.7.2 Pharmacokinetics Sample Analysis

Sample analysis will be performed by Alturas Analytics (Moscow, Indiana USA) under the direction of Cortendo AB. Concentrations of levoketoconazole (2S,4R-ketoconazole) in plasma will be determined using current validated methodology.

6.5 Additional Considerations for Risk Management

6.5.1 Instructions for Subjects

Subjects will be instructed to always carry a card and/or other identifier (e.g. bracelet or pendant) 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 suggestive of adrenal insufficiency. 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.

6.5.2 Considerations for the Investigator

Subjects in the TM Phase will be contacted (method by subject preference) approximately 1 week after taking the first dose (DL1) and approximately 1 week after each dose adjustment (DL0, DL2, and DL3) to check on subject status and ensure compliance with medication administration. During the TM Phase, subjects will be asked to return to the clinic or will be visited by a qualified HHC professional for one extra safety evaluation 5 days (± 2 days) after each dose adjustment when the total daily dose is 750 mg/day or above.

In the Restoration Phase, subjects will be contacted (method by subject preference) weekly between study visits.

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 H for testing recommendations.

- Hypertension: See Appendix I for guidelines for classification of blood pressure levels and follow-up recommendations.
- Hypocortisolemia: See Appendix K for evaluations of signs and symptoms.
- Hypomineralocorticoidism: See Appendix K for evaluations of signs and symptoms.
- Hypogonadism: See Appendix K 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 K). 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 the following section (Section 6.5.3) for assessment of signs and symptoms of adrenal insufficiency and Appendix K for evaluation of signs and symptoms of adrenal insufficiency.

6.5.3 Adrenal Insufficiency

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.

It is well recognized that subjects with a good response to treatment for CS resulting in decreased, but not necessarily low, cortisol concentrations may exhibit signs and symptoms of adrenal insufficiency (a non-life-threatening condition) that can mimic those associated with acute adrenal crisis, which is a life-threatening event warranting immediate medical intervention. Therefore, discrimination between the two conditions may not be readily evident by history or physical examination. Furthermore, subjects may have adrenal insufficiency without abnormal cortisol concentrations, if the cortisol response is 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.

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 (if possible early-morning serum cortisol). Laboratory evidence of hypoadrenalism (or

hypocortisolism) is defined as morning serum cortisol level less than 3 µg/dL. Even if serum cortisol and/or 24-hour UFC are within the normal laboratory reference range, the possibility of adrenal insufficiency should be considered based on other clinical signs and symptoms. Please see Appendix K for a fuller list of clinical signs and symptoms;

- Random glucose and electrolytes;
- Lying and standing (i.e. orthostatic or postural) blood pressure measurements and pulse to evaluate postural changes;
- Full review of systems.

Should mild adrenal insufficiency be deemed confirmed or probable, study medication should be temporarily withheld. For moderate or severe symptoms/signs, study medication should be temporarily withheld and rescue corticosteroids administered until adrenal insufficiency and its underlying trigger, if one is identified, has abated and the subject is stable. Study medication, potentially administered at a lower dose if the event occurs during the TM Phase, may be restarted once the clinical situation allows. If adrenal insufficiency is suspected and the subject is taking the lowest levoketoconazole 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.

All cases of suspected adrenal insufficiency, whether eventually considered to be drug-related or not, should be reported as AESIs to Chiltern Pharmacovigilance (Section 13.7).

7 LIFESTYLE AND DIETARY RESTRICTIONS

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

- Consumption of grapefruit, lime juice and Seville oranges (aka sour orange, bigarade orange, or marmalade orange) and its products should be avoided;
- Genuine licorice (not the same as licorice-flavored candy) should be avoided or consumed in small amounts infrequently;
- Consumption of excessive alcohol should be avoided (note: there is no known safe amount in relation to use of levoketoconazole);
- Donation of blood or blood products is prohibited during the study.

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
    - 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
    - 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
    - Smoking cigarettes, pipe, cigar or any other substance.

Information on each subject's job related working shift and sleep hours will be collected.

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 (HDPE) bottles. Refer to the Pharmacy Manual for details of labeling of the investigational product.

8.2 Description of Reference Therapy

An active reference therapy will not be used. Placebo tablets will be supplied to ensure adequate concealment of study treatments during the Randomized Withdrawal Phase and Restoration Phase.

Placebo tablets identical in appearance to levoketoconazole will be administered during the Randomized Withdrawal Phase using the same regimen as the Therapeutic Dose of levoketoconazole established during the TM Phase (levoketoconazole-naïve cohort) or at study entry (SONICS-completer cohort). During the Restoration Phase, blinded placebo to be added onto a levoketoconazole regimen will be started at 1 tablet BID and titrated every 2 days in 1 tablet increments per Table 2 until the Therapeutic Dose-equivalent is achieved unless the Therapeutic Dose is DL0. The total final tablet count (active + placebo) during Restoration Phase will equal twice the total tablet count of the Therapeutic Dose, not to exceed 8 tablets BID.

8.3 Dosage and Administration

Levoketoconazole or placebo tablets will be administered BID, approximately every 12 hours, per the titration scheme described in Section 4.2.2.2. For the levoketoconazole-naïve cohort, the total daily dose will be titrated in 150 mg increments from a starting dose of 300 mg (dosed as 150 mg BID) up to a maximal daily dose of 1200 mg (dosed as 600 mg BID) until a Therapeutic Dose is established. The minimum daily dose is 150 mg QD for subjects who cannot tolerate 150 mg BID. For subjects in the SONICS-completer cohort, the Therapeutic Dose will have been established prior to enrollment in this study and confirmed in the screening phase. For subjects in the levoketoconazole-

naïve cohort, the Therapeutic Dose will be established by the end of the TM Phase. The Therapeutic Dose will be used as the target dose and dose-regimen during the Restoration Phase.

Subjects will receive an adequate amount of the investigational product at each 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, which affects gastric acidity, in relationship to dosing is not recommended, especially during dose titration, as doing so might lead to excessive variability in levoketoconazole blood levels and thus a variable response to therapy.

8.3.1 Dose Rationale

The effects of treating CS with any therapeutic agent is not generally predictable *a priori*. Ketoconazole a commonly used therapeutic agent has variable PK and is titrated to effect up to levels as high as 1800 mg daily to control severely ill CS patients. In most patients responsive to ketoconazole, doses average approximately 600 to 800 mg/day with the range of 200 to 1800 mg having been utilized to achieve normalization of cortisol levels [Nieman 2002, Pozza 2012].

Like ketoconazole, levoketoconazole is not expected to be administered at a fixed dose but will be titrated to effect in each subject. Levoketoconazole has been used in clinical trials up to a dose of 1200 mg daily. The highest dose of 600 mg BID levoketoconazole (1200 mg total daily dose) is used during this study, because some CS subjects may require higher levels of cortisol suppression to achieve adequate therapeutic response. Doses of levoketoconazole higher than 300 mg BID (600 mg total daily dose and higher) will be guided by enhanced tolerability and safety monitoring as described in Section 4.2.2.4. It is expected that titration to the highest dose will be the exception rather than the norm, based on prior experience with levoketoconazole in SONICS and nonclinical comparisons with ketoconazole. A detailed description of nonclinical and prior clinical data with levoketoconazole and rationale for dose selection is provided in the Investigator's Brochure.

8.3.2 Dose Titration and Maintenance (TM) Phase (levoketoconazole-naïve cohort)

For levoketoconazole-naïve subjects and subjects who completed the M12 visit of SONICS who have not received a stable Therapeutic Dose of levoketoconazole for the 12 weeks immediately preceding Screening, open-label levoketoconazole will be titrated to find an effective and tolerable dose for each subject (i.e. the Therapeutic Dose).

The total daily dose will be titrated in 150 mg increments from a starting dose of 300 mg (dosed as 150 mg BID) up to a maximal daily dose of 1200 mg (dosed as 600 mg BID) until a Therapeutic Dose is established (Section 4.2.2.2.2). Subjects re-establishing the Therapeutic Dose via re-titration may begin titration at their current or most recently received dose at the discretion of the Investigator.

The minimum daily dose is 150 mg QD for subjects who cannot tolerate 150 mg BID. For subjects in the levoketoconazole-naïve cohort, the Therapeutic Dose must be established by the end of the TM Phase.

For subjects in the SONICS-completer cohort, the Therapeutic Dose will have been established prior to enrollment in this study and will be confirmed at screening, prior to randomization.

8.3.2.1 Dosage Changes During TM Phase

During the TM Phase (while treatment is open-label), once the Therapeutic Dose is achieved, the dose should generally not be further adjusted if the UFC levels are within normal limits. However, the dose may be increased if medically necessary to maintain eucortisolemia or decreased to address drug intolerance or AE. The Therapeutic Dose must be stable (i.e. fixed), with normal mUFC established, for at least 4 weeks before a subject may be eligible for the Randomized Withdrawal Phase.

8.3.2.2 Dosage Reductions and Use of Dose Level 0

Dose reductions are allowed and should be used judiciously to manage certain AEs. The following AEs are AESIs for which dose reductions can sometimes be helpful:

- Suspected or confirmed adrenal insufficiency (see Section 6.5.3);
- Liver safety test abnormalities (see Section 5.4.2);
- QTc prolongation (see Section 6.4.6.2).

Generally, if levoketoconazole is restarted during the TM Phase following an AESI, the dose should be reduced to the dose level (i.e. one dose level) lower than that associated with the AESI to mitigate the risk of future occurrences of the event (as described in Section 4.2.2.3). Further titration is subsequently allowable if the Investigator, in consultation with the Medical Monitor, believes that the risk of AESI recurrence is outweighed by the expected benefit of the higher dose, as supported by evidence from disease-related measures.

If a suspected drug-related AESI is associated with the lowest usual dose level (DL1, 150 mg BID), the subject may receive the lowest possible dose of 150 mg QD (DL0) following discussion with the Medical Monitor. Subjects in the TM Phase may subsequently resume the titration scheme if DL0 is not a Therapeutic Dose but a partial cortisol response is evident and there was evidence of a better response at DL1. Discussion of the benefits and risks of resuming titration with the Medical Monitor is required in such cases.

The 150-mg dose for DL0 should be administered in the evening, except on the day of the in-clinic or at-home procedures, when the dose should be administered during the visit to allow for post-dosing ECG and PK assessments.

Subjects who experience an AESI during the Randomized Withdrawal or Restoration Phase cannot reduce the dose of study medication, which is blinded. However, study medication may be temporarily withheld and subsequently resumed at the prior dose once

the AE resolves, if the Investigator believes that continued use of the study medication remains in the subject's best interest.

8.3.3 Randomized Withdrawal Phase and Restoration Phase

8.3.3.1 Blinding

A randomized, double-blind, placebo-controlled design will be used in the Randomized Withdrawal Phase and the Restoration Phase of the study. The Investigator, study site personnel, representatives of the Sponsor and the Contract Research Organization (CRO) involved in the monitoring, data management, analysis, and other aspects of the study will be blinded to the randomized treatment assignments during the Randomized Withdrawal Phase and Restoration Phase. Some individuals, not involved in the conduct of the study, will be unblinded for a planned interim analysis after all subjects have either completed the Randomized Withdrawal Phase or discontinued prior to the end of the Randomized Withdrawal Phase. The rest of the individuals involved in the study will remain blinded at the individual subject level until after the database lock at the end of the study, except as described below. Details on the interim analysis are provided in Section 12.6.

The TM Phase is open-label. Subjects who require early rescue during the Randomized Withdrawal Phase may receive open-label levoketoconazole and continue in the study.

The investigational product and reference therapy are identical in appearance and the packaging and labelling will be identical to keep the study blinded during the Randomized Withdrawal Phase and the Restoration Phase (including when early rescue is needed).

For the Randomized Withdrawal Phase and the Restoration Phase, treatment-code breaks should occur only in exceptional circumstances when knowledge of the actual treatment is essential for further management. Investigators are encouraged to discuss with the Clinical Research Organization (CRO) Medical Monitor if they believe that unblinding is necessary and, in any case, Investigators or other responsible site personnel must report unblinding to the Sponsor via telephone/email as soon as feasible after the event. If unblinding is deemed to be necessary, the Investigator should use the main system for emergency unblinding through the interactive randomization system via interactive response technology (IRT).

Treat as indicated. If unblinding cannot be completed promptly, treatment of the subject or other affected person should proceed as if the ingested medication were levoketoconazole.

Investigators are encouraged to maintain the blind except as needed to manage the emergency, whether the emergency involves the subject or someone outside of the study who was exposed to the study medication (e.g. a child who ingests the study medication). Treatment allocation must NOT be disclosed to the subject and/or other study personnel including other site personnel, monitors, and Sponsor or CRO staff, nor should there be any written disclosure of the code in any of the corresponding source documents. The Investigator must report all treatment-code breaks (with reason) as they occur on the corresponding CRF page. Treatment allocation information after a code break should be

held by the designated person at site and by the CRO Global Safety Officer for the study or designee. Unblinding should not necessarily be a reason for study drug discontinuation. Investigators are responsible for promptly notifying the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) in cases involving a treatment-code break.

For purposes of reporting certain AEs to competent authorities, IRBs/IECs, and certain responsible Investigators, the Sponsor will designate personnel who will have access to information on unblinded study treatment. Safety signal evaluation and trend analysis will remain the responsibility of the Sponsor, as described in the safety monitoring plan and DSMB charter.

8.3.3.2 Randomization and Treatment Assignment

At the beginning of the Randomized Withdrawal Phase (Visit RW0) eligible subjects will be randomly assigned in a 1:1 ratio to receive either:

- Group 1: Levoketoconazole tablets in the same regimen as the Therapeutic Dose
- Group 2: Matching placebo tablets in the same regimen as the Therapeutic Dose.

The Therapeutic Dose will be used as the target dose and dose-regimen during the Restoration Phase. Treatments in this phase will continue to be double-blind. Subjects will continue receiving the same treatment as in the Randomized Withdrawal Phase and will receive additional rescue treatment with either:

- Group 1: Placebo tablets
- Group 2: Levoketoconazole tablets.

The starting Restoration Phase dose will be one tablet BID and the dose will be titrated in one tablet increments every 2 days until the Therapeutic Dose-equivalent tablet count is achieved unless the Therapeutic Dose is DL0.

8.3.3.3 Early Rescue

Subjects who require early rescue during the Randomized Withdrawal Phase may receive open-label levoketoconazole. The rapid titration schedule of the Restoration Phase should be used to reestablish the Therapeutic Dose of open-label levoketoconazole used for the early rescue. Dose adjustments may be made, as medically indicated, after rapid re-titration. This includes adjustments to dose levels above the previous therapeutic dose if required to return subject to eucortisolemia. During early rescue, the titration will increase in 1 tablet increments every 2 days alternating AM and PM per Table 2.

9 DRUG SUPPLIES, DISPENSING, STORAGE AND ACCOUNTING

9.1 Product Storage

Levoketoconazole and matching placebo tablets should be stored at 15°C to 25°C (59°F to 77°F).

9.2 Investigational Product Accountability

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 and returned to Cortendo AB (when applicable), the amount supplied and/or administered to and returned by subjects, if applicable.

9.3 Compliance Assessment

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. In addition, subjects should bring all empty medication bottles and unused medication with them to all in-clinic visits except for additional safety visits required in the TM Phase. Drug accountability to determine compliance will be performed at all other in-clinic visits. Drug accountability will not be performed during visits by HHC professional.

9.4 Treatment of Investigational Product Overdose

There is no known direct antidote to levoketoconazole once absorbed. However, if 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).

Refer to Section 4.2.2.4 for additional safety monitoring for administration of daily doses 750 mg/day or above.

10 CONCOMITANT MEDICATIONS

10.1 Permitted Medications

For management of dyslipidemia, pravastatin, fluvastatin, pitavastatin and rosuvastatin are the only allowed “statins”. For subjects for whom lipid reduction therapy is being considered, all lipid lowering drugs should be added and stabilized for at least 4 weeks prior to TM0 for the levoketoconazole-naïve cohort or RW0 for the SONICS-completer cohort, as improvements in lipids are being assessed as an endpoint for levoketoconazole treatment in this study.

For management of hypokalemia, potassium supplements are encouraged. It is advised that maintenance of serum potassium levels within the normal range and above 4.0 mmol/L may reduce the risk of drug-induced QTc prolongation.

Most medications used to treat T2DM are allowed. Metformin is allowed, although its levels might be increased by levoketoconazole. Routine monitoring of glucose, 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 list will be provided.

Most commonly used treatments for osteopenia or osteoporosis—excluding certain hormonal treatments—are allowed. Calcium should be taken at least 2 hours after ingesting study medication.

All medications should be scrutinized during Screening, using Appendix J as a guide and with help from the Medical Monitor if needed. Medication additions or switches after Screening should be kept to a minimum and should likewise prompt a check against Appendix J, 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, anti-inflammatory, 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 J. 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);
- Statins other than pravastatin, fluvastatin, pitavastatin and rosuvastatin; potentially eligible subjects should be switched to an allowed statin (or other allowed therapy) several weeks prior to the Baseline Visit for the TM Phase (Visit TM0) whenever feasible to allow equilibration of blood lipids (Note: new lipid lowering medications should not be added after the screening period as described in Section 10.1);
- Carbamazepine, fenofibrate (assay interference), carbenoxolone;
- Genuine licorice (mineralocorticoid effects);
- Steroidogenesis inhibitors or dopamine agonists (interference with drug effect, Appendix J, Table 12 and Table 13);
- Megestrol acetate or medroxyprogesterone acetate and selected other synthetic progestins (see Appendix J, Table 14) [Schindler 2003];

- Any other drug treatments used to lower cortisol in CS that are subject to washout (see Section 5.2 and Appendix J, Table 15) are prohibited throughout the study;
- Weight loss medications (either prescription or over the counter, Appendix J, Table 16);
- Drugs whose systemic exposure is potentially increased significantly by concomitant use of levoketoconazole (Appendix J, Table 18);
- 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 J, Table 19);
- Medications resulting in QTc prolongation as a direct effect or because of interaction with levoketoconazole, examples include: cisapride, dofetilide, pimozide, quinidine. (Appendix J, Table 20). However, in selected cases where no alternative medications are available, permission from the Medical Monitor may be sought;
- Topical or inhaled corticosteroid preparations (interference with drug effect, Appendix J, Table 12);
- The following herbal medicines: St John's Wort, echinacea, gingko, goldenseal, yohimbe, red rice yeast, danshen, silybum marianum, Asian ginseng, schissandra sphenanther, shankhapushi, and Asian herb mixture (Xiao chai hu tang and Salboku-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 J, Table 23). 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 J, Table 21).

11 SUBJECT COMPLETION AND WITHDRAWAL

11.1 Subject Completion

Subjects who complete the end of the Restoration Phase (Visit RES2) of the study, regardless of their response status, will be considered to have completed the study and are eligible for inclusion into the OPTICS Study.

Subjects who receive early "rescue" will also be considered to have completed the study and are eligible for inclusion into the OPTICS Study.

11.2 Subject Withdrawal Procedures

All premature study withdrawals and their causes must be documented, to include the specific reason(s) prompting withdrawal, by the Investigator on the CRF, and, if need be, on the AE form.

If the subject chooses to withdraw or is otherwise withdrawn before completing the study, the Investigator should make every attempt to have the subject return to the clinic to complete safety and PK assessments as outlined in the Schedule of Events for the TM7 Visit (if in the Dose Titration and Maintenance Phase), the RW5 Visit (if in the Randomized Withdrawal Phase) or the RES2 Visit (if in the Restoration Phase) in Appendix A. All data gathered on the subject prior to termination will be made available to the Sponsor.

12 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

12.1 Populations for Analysis

Intent-to-Treat Population (ITT): The ITT population will include all subjects who are randomized and receive at least one dose of blinded study medication during the Randomized Withdrawal Phase. The ITT population will be used for the primary analysis of efficacy and secondary analyses of efficacy and safety.

Per Protocol (PP) Population: The PP population will consist of all subjects in the ITT population who have no major protocol deviations during the Randomized Withdrawal Phase that could affect the primary endpoint. This population will be used in supportive analyses of the primary endpoint and secondary efficacy endpoints.

Levoketoconazole-naïve Population: The levoketoconazole-naïve population will consist of all subjects in the levoketoconazole-naïve cohort (defined in Section 4.1) who receive at least one dose of study medication during the Dose Titration and Maintenance Phase. This population will be used for supportive evaluations of safety and for exploratory efficacy, safety, and PK analyses.

SONICS-completer Population: The SONICS-completer population will consist of all subjects in the SONICS-completer cohort (defined in Section 4.1) who receive at least one dose of blinded study medication during the Randomized Withdrawal Phase. This population will be used for supportive evaluations of safety and for exploratory efficacy, safety, and PK analyses. Because only a minority of the subjects are anticipated to be in

the SONICS-completer cohort, the analyses will be performed only if the size of this cohort is at least 30% of the ITT population.

12.2 Hypothesis

The primary endpoint for this study is the proportion of subjects with loss of therapeutic response to levoketoconazole upon withdrawing to placebo compared with continued levoketoconazole treatment. Loss of response is based on the mean of three 24-hour UFC measurements (mUFC) obtained at any visit from second through final randomized-withdrawal visits (RW1 through RW5 inclusive) when:

- mUFC is more than 1.5X the ULN of the central laboratory's reference range OR
- mUFC is more than 40% above the Baseline (RW0) value if the RW0 value was 1.0X ULN or greater for SONICS-completer cohort subjects OR
- an early rescue criterion is met.

The null hypothesis is that the proportion of subjects with loss of response upon withdrawing to placebo compared with continued levoketoconazole, as defined above, is not different between levoketoconazole and placebo. The alternative hypothesis is that the two proportions are different, specifically that there is an increased loss of response for the placebo arm.

12.2.1 Sample Size Determination

For the purpose of sample size estimation, it is assumed that among subjects in the ITT population who complete at least the RW4 visit in the Randomized Withdrawal Phase, 10% will lose therapeutic response in the levoketoconazole arm vs. 75% in the placebo arm. The 10% loss of therapeutic response rate in the levoketoconazole arm is based on data from the SONICS study.

For the analysis of the primary endpoint, subjects in the ITT population who withdraw prior to RW4 are considered as losing therapeutic response. As such, the assumed loss of therapeutic response rate in the overall ITT population in each arm depends on the withdrawal rate prior to RW4 during the Randomized Withdrawal Phase. It is expected that the withdrawal rate will be no more than 10%, but up to 20% is considered in the sample size estimation. If the withdrawal rate is 10% per arm, a sample size of 46 subjects (23 per arm) randomized and treated during the Randomized Withdrawal Phase corresponds to 42 subjects (21 per arm) completing RW4 and provides approximately 99% power, using two-sided Fisher's Exact test, to detect the alternative hypothesis of a loss of therapeutic response rate of 17% in the levoketoconazole arm and 78% in the placebo arm vs. the null hypothesis of no difference between the two arms. If the withdrawal rate is 20% per arm, a sample size of 54 subjects (27 per arm) randomized and treated during the Randomized Withdrawal Phase corresponds to 44 subjects (22 per arm) completing RW4 and provides approximately 98% power to detect the alternative hypothesis of a loss of therapeutic response rate of 26% in the levoketoconazole arm and 81% in the placebo arm vs. the null hypothesis of no difference between the two arms.

Because enrollment into the Dose Titration and Maintenance Phase will be closed prior to the last subject being randomized and treated in the Randomized Withdrawal Phase, the actual sample size for the Randomized Withdrawal Phase is not prespecified. The timing of enrollment closure will be based on the rolling 4-week completion rate trend for the Dose Titration and Maintenance Phase. A minimum of 46 subjects (23 per arm) and a maximum of 54 subjects (27 per arm) will be targeted to be enrolled into the Randomized Withdrawal Phase based on the observed withdrawal rate trend for the phase.

A minority of randomized subjects are anticipated to be in the SONICS-completer cohort. Any subject who withdraws after randomization will not be replaced. Withdrawn subjects will not be re-entered into the study.

12.3 General Considerations 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, race) will be summarized using the number of observations (n) and percentage in each category.

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

12.4 Study Completion, Premature Withdrawal and Missing Data

Definition of Study Completion

Study completion for purposes of assessing the primary endpoint is defined as either of the following:
(1) having completed Visits RW0 (Randomized Withdrawal Baseline) and RW5 (i.e. final scheduled visit in Randomized Withdrawal Phase) regardless of UFC status OR
(2) having completed RW0 and having met criteria for use of early rescue treatment with open-label levoketoconazole (or another rescue medication) after RW0.

Definition of Non-completion

Subjects withdrawn from the study without meeting the definition of study completer above will be considered as prematurely withdrawn (i.e. non-completers). All available data for subjects who are study non-completers will be included in all analyses.

Missing or Inadequate UFC Collections

At any visits for which **three** 24-hour urine samples for UFC determination are scheduled to be collected, **at least two** UFC collections must be deemed adequate to be able to derive a mUFC value and thus be considered as non-missing. When **more than two** UFC collections are made only those collections deemed adequate by the Sponsor will be included in the calculation of the mUFC.

Study non-completion, reasons for non-completion, and missing or inadequate collections for determination of UFC will be summarized.

Handling of Missing Data for Analyses of the Primary Endpoint

The following rules will be applied for determining loss of therapeutic response when

some or all mUFC data are missing:

1. A subject withdraws prematurely during the Randomized Withdrawal Phase (i.e. Visit RW5 is not completed nor is the subject in need of early rescue treatment) and no post-randomization adequate mUFC determination is available. In this case, the subject will be assumed to have lost therapeutic response; OR
2. A subject withdraws prematurely during the Randomized Withdrawal Phase after RW0 and before RW5, with no early rescue, and at least one post-randomization mUFC determination is available. In this case, if the latest available adequate mUFC determination is the one for RW4, all available mUFC determination(s) will be used to determine if loss of therapeutic response occurred for that subject, but if the latest available mUFC determination is for a visit before RW4, the subject will be assumed to have lost therapeutic response; OR
3. A subject completes the Randomized Withdrawal Phase with one or more missing adequate mUFC determinations, with at least one post-randomization adequate mUFC determination available. In this case, if the latest available adequate mUFC determination is the one for RW4 or RW5, all available mUFC determination(s) will be used to determine if loss of therapeutic response occurred for that subject, but if the latest available mUFC determination is for a visit before RW4, the subject will be assumed to have lost therapeutic response.

Supportive analyses of the primary endpoint that require more than one adequate mUFC determination during the Randomized Withdrawal Phase to be available will be performed. For the secondary and exploratory efficacy endpoints, at-visit analyses will be performed using longitudinal models without imputation as the primary approach; where specified; imputations to replace missing values will be considered as supportive. Details will be provided in the Statistical Analysis Plan (SAP).

12.5 Final Analyses

12.5.1 Definitions of Baseline

For the purposes of analyzing changes and shifts from Baseline, whether for safety or efficacy evaluations, two Baselines will be used, depending on the analysis population and the assessment timing. The levoketoconazole-naïve analysis population has its own Baseline at Visit TM0 (including values obtained during Screening that are within 3 weeks of TM0). The TM0 Baseline will primarily be used to infer changes and shifts that occur during the TM Phase only. Both the levoketoconazole-naïve and SONICS-completer analysis populations will use as Baseline Visit RW0, which is applicable to assessments that are made during the Randomized Withdrawal Phase and the Restoration Phase, such as the analysis of primary efficacy.

Thus, for most measures, analytical summaries will be created using two Baselines when the levoketoconazole-naïve population is involved and one Baseline when only the SONICS-completer population is involved or when the analysis is concerned with the post-randomization period only (e.g. the primary efficacy analysis). For some endpoints analyzed during the Restoration Phase only, there may be interest in looking at the changes and shifts from the start of the Restoration Phase for the subset of subjects who

were randomized to placebo for the Randomized Withdrawal Phase and received levoketoconazole during the Restoration Phase. In such analyses, the Baseline of interest will be Visit RW5. If the Baseline is not obvious, care will be taken to describe the specific Baseline used in the description of the analysis.

12.5.2 Safety Analyses

The final analysis of safety will be coincident with the last subject visit following completion of the Restoration Phase.

Safety analyses will be conducted by study phase and/or by time point, as applicable. Adverse events will be recorded from the date that informed consent was signed. Treatment-emergent adverse events (TEAEs) will be summarized and reported by pooled-cohorts and separately by SONICS-completer and levoketoconazole-naïve cohorts.

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 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.

An independent DSMB will review all SAEs and AESIs on a rolling basis and assess benefits and risk of therapy (unblinded) systematically at approximately 6-month intervals. The timing of the first bi-annual DSMB meeting may be adjusted based on subject accrual. There are no plans to stop the study prior to completion based on these reviews, and therefore no stopping rules will be created. The DSMB will not report its findings other than to indicate whether the protocol must be changed for the study to continue as planned or otherwise make recommendations designed to ensure subject safety and study integrity. Details of the DSMB procedures will be described in a separate charter.

12.5.2.1 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. Drug exposure will be calculated separately for each analysis population (Section 12.1).

Study drug compliance at each study phase and cumulative study drug compliance for the study overall 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.

For subjects in the levoketoconazole-naïve cohort, study medication dose levels will be listed by visit and days on study, with the Therapeutic Dose indicated. All study medication interruptions or permanent discontinuations prompted by the Investigator or Sponsor will be listed for each subject, along with the medication identity, timing and reason.

12.5.2.2 Adverse Events (AEs)

All 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].

The 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% per treatment group) in pooled levoketoconazole and placebo groups will also be reported.

TEAE summaries will include frequency by treatment group (pooled levoketoconazole), levoketoconazole dose (individual dose level) and relative onset time (by visit, by Phase, by study days, by days in Phase, etc.), depending on the analysis population. Additional summaries and listings will be created to explore TEAE signals.

12.5.2.3 Clinical Laboratory Evaluations

A laboratory value that is within the central laboratory's reference range will be considered normal. A laboratory value that is outside the central laboratory's normal range will be considered abnormal. 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.

Liver function tests will be further summarized descriptively using modified eDISH plots and other displays.

Further descriptions of laboratory analyses will be included in the SAP.

12.5.2.4 Vital Signs

Heart rate, SBP and DBP will be measured in triplicate at least 3 minutes apart 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 (RW0) for each measurement at each visit will be summarized by treatment group and by dose of levoketoconazole. In addition, values of clinical importance (Table 5) will be identified in the data listings.

Table 5 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)

12.5.2.5 Electrocardiograms (ECGs) and QTc Intervals

Summary ECGs, based on the measurement of an ECG over 1 to 5 minutes as described in Section 6.4.3 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 (RW0) will be summarized descriptively by dose, treatment group and time point. ECG results will be available to the Investigator shortly after being obtained and all ECGs will be reviewed by a central consulting cardiologist who will provide an "over-reading" that will serve as the definitive study value. While on study treatment, a QTc above 500 msec or above 60 msec above Baseline will be an AESI (See Section 13.2.2).

Categorical changes from Baseline and QTc values from each visit will be summarized by worst change, by visit, by treatment group and by dose of levoketoconazole. The clinically important categories (Table 6) of actual and change values will be tabulated and provided as listings.

QTc intervals will be assessed using paired t-tests of change values and QTc shifts from normality will be assessed by McNemar's test. All other analyses will be descriptive.

Table 6 QTc Interval Values of Clinical Importance

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

12.5.2.6 Oral Glucose Tolerance Test (pre-diabetic subjects with IFG)

For pre-diabetic subjects with IFG at Baseline, the number and percent of subjects after each study Phase will be summarized for each of the following categories.

Pre-test:

- Normal: glucose level < 100 mg/dL (5.6 mmol/L)
- Impaired fasting glucose: glucose level ≥ 100 mg/dL (5.6 mmol/L) and < 126 mg/dL (7.0 mmol/L);

Post-test:

- Normal: 2-hour glucose level below 140 mg/dL;
- Impaired glucose tolerance (pre-diabetic): glucose level at least 140 mg/dL and no more than 200 mg/dL;
- Provisional diagnosis of diabetes (diabetic): glucose level at least 200 mg/mL.

Glucose and insulin values during the OGTT will also be summarized by maximum value, time to maximum value and AUC, and statistically analyzed with a paired t-test for each assessment. Exploratory analyses of insulin resistance and/or beta cell function will be described in the SAP. Changes in OGTT-derived glucose values from Baseline (RW0) to RW5 and from Visits RW5 to RES2 will be summarized by treatment group.

12.5.2.7 Other Safety Measures

All other safety laboratory measures (e.g. morning serum cortisol, ACTH, prolactin, testosterone, urine albumin:creatinine) will be listed by subject and time point and descriptively summarized, including changes from Baseline (RW0) by treatment group and dose of levoketoconazole.

Changes in the size of pituitary tumor (in millimeters of largest diameter and/or by estimated volume) from Screening to Baseline (RW0) and RW5 (for the levoketoconazole-naïve cohort) and from Baseline (RW0) to RW5 (for the SONICS-completer cohort) will be summarized descriptively by treatment group.

12.5.3 Efficacy Analyses

The ITT population (i.e. pooled cohorts) will be used in the main analyses of the primary endpoint and the PP population in supportive analyses. Handling of missing data for primary endpoint analyses is described in Section 12.4. Exploratory efficacy analyses will also include the levoketoconazole-naïve and SONICS-completer populations.

12.5.3.1 Primary Efficacy Analysis

Loss of Therapeutic Response

Mean UFC data obtained at Visit RW0 serves as the Baseline measure defining cortisol response. As an entry requirement, all subjects who are enrolled into the Randomized

Withdrawal Phase will have achieved a therapeutic cortisol response (though not necessarily a normalized mUFC if a SONICS-completer cohort subject) and will be taking an established dose of levoketoconazole, the Therapeutic Dose. Considerations for loss of established cortisol response during the Randomized Withdrawal period makes an allowance for the subgroup of SONICS-completer cohort subjects who do not have a normalized mUFC response at RW0.

Loss of response is assessed based on the mean of **three** 24-hour UFC measurements (mUFC) (at least two measurements from adequate collections) obtained at any visit from the second through the final Randomized Withdrawal visits (RW1 through RW5 inclusive) when:

- The mUFC is above 1.5X the ULN of the central laboratory's reference range; OR
- The mUFC is over 40% above the Baseline (RW0) value if the RW0 value is above the ULN (i.e. >1.0X ULN) for SONICS-completer cohort subjects; OR
- An early rescue criterion is met.

The primary efficacy analysis will determine the significance of the difference in proportions of subjects losing response among each of the two blinded treatment groups.

Statistical significance testing will be conducted using a logistic regression model containing fixed effect terms for Randomized Withdrawal treatment group (levoketoconazole, placebo) and subject cohort (levoketoconazole-naïve cohort, SONICS-completer cohort) and confirmed using a two-sided Fisher's Exact test.

12.5.3.2 Secondary Efficacy

Inferences derived from secondary efficacy analyses will be gated on results from the primary efficacy analysis. Secondary efficacy analyses will be hierarchically structured to ensure control of the family-wise type I error rate at the 0.05 level. Hypothesis tests for secondary endpoints will be based on null hypotheses that assume no *a priori* differences between placebo and levoketoconazole treatments. All secondary endpoints will be analyzed using the ITT population (primary analyses) and the PP population (supportive analyses, but only if PP population is notably different from ITT population, see SAP for details).

Additional details of the testing procedures not included here, including handling of missing data, will be described in a SAP to be finalized prior to breaking the blind.

UFC and LNSC Analyses

Changes in UFC and LNSC from Baseline

Mean UFC will be calculated from adequate 24-hour urine collections only. At Baseline (RW0) and at end of Randomized Withdrawal Phase and of Restoration Phase, where three samples are to be collected, the mUFC will be calculated only if there are at least two adequate samples. When the number of adequate samples is less than two at any visit, the main secondary analyses will consider the UFC value as missing; sensitivity

analyses will use a single adequate urine sample or imputations of missing values. The mUFC from the collections at each visit will be used in the analysis of UFC.

Mean UFC and LNSC will be summarized by time point using descriptive statistics and displayed over time. Changes from Baseline (RW0) in mUFC and LNSC during the Randomized Withdrawal Phase will be analyzed using a repeated measures mixed effects model with fixed effect terms for treatment group, subject cohort, time (i.e. visit), and treatment-by-time interaction, with Baseline value as a covariate and subject as a random effect. The treatment groups will be compared using least squares mean differences between treatment groups and associated 95% CIs for each time point will be derived from the model. These CIs will be regarded as descriptive statistics. Two-sample t-tests will also be performed to compare the two treatment groups for the mean change from Baseline to each nominal visit during the Randomized Withdrawal Phase.

Normalization of UFC during Restoration Phase

The number and proportion of subjects with normalization of mUFC at RES2 is defined as the proportion of subjects with abnormal mUFC at RW5 whose mUFC is at or below the ULN of the reference range at RES2. Normalization of mUFC at RES2 will be calculated for each treatment group and presented as shift tables from RW5 to RES2 using three strata of mUFC status at or below ULN, more than ULN and no more than 1.5X ULN, above 1.5X ULN.

Normalization of UFC at the end of Randomized Withdrawal Phase

The number and proportion of subjects in the Randomized Withdrawal Phase with mUFC normalization (at or below ULN) at the end of Randomized Withdrawal Phase (RW5) will be summarized for each treatment group and compared using Fisher's Exact test (with corresponding 95% CIs).

CS Comorbidity Biomarkers

The changes from Baseline (RW0) and percentage change from Baseline in individual biochemical markers of CS comorbidities (fasting glucose, fasting insulin, HOMA-IR, HbA1c, total cholesterol, LDL-C, and hsCRP) during the Randomized Withdrawal Phase and the Restoration Phase will be summarized by treatment group and time point and assessed using two-sample t-test comparison at each visit in the Randomized Withdrawal Phase. In addition, shifts from Baseline (with regards to laboratory normal range) in individual biochemical markers of CS comorbidities will be summarized at each scheduled visit.

For CS comorbidities measured at more than one visit after RW0 during the Randomized Withdrawal Phase, changes from Baseline during the Randomized Withdrawal Phase will also be analyzed using a repeated measures mixed effects model with fixed effect terms for treatment group, time (i.e. visit), and treatment-by-time interaction, the concurrent CS medical conditions (e.g. diabetes, hypertension) as Baseline covariates and with subject as a random effect. Least squares mean differences between treatment groups and associated 95% CIs for each time point will be derived from the model. These CIs will be regarded as descriptive statistics.

Cushing's Syndrome Quality of Life Questionnaire

QoL (Appendix L) measures and changes from Baseline (RW0) at the end of the Randomized Withdrawal Phase and Restoration Phase will be summarized by treatment group and time point using descriptive statistics and analyzed using two-sample t-test at the end of the Randomized Withdrawal Phase.

Beck's Depression Questionnaire

Changes from Baseline (RW0) for the Beck's Depression questionnaire (Appendix N) at the end of the Randomized Withdrawal Phase and Restoration Phase will be summarized by treatment group and time point using descriptive statistics and analyzed using two-sample t-test at the end of the Randomized Withdrawal Phase.

Acne, Hirsutism and Peripheral Edema

Acne, hirsutism (for females only) and peripheral edema scores will be calculated as per their respective instrument-derived instructions, provided in Appendix M, and results will be summarized at each visit, including changes from Baseline and score shifts from Baseline. Changes from Baseline during the Randomized Withdrawal Phase and Restoration Phase will be summarized by treatment group and time point and mean changes from Baseline assessed using two-sample t-test at each visit in the Randomized Withdrawal Phase.

12.5.3.3 Exploratory Efficacy

Medication Changes

Changes to concomitant medications (focusing on, but not necessarily limited, to anti-hypertensive, anti-hyperglycemic, anti-cholesterol and anti-inflammatory medications) will be listed by subject. The number and proportion of usage of each medication class 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 treatment group and time point. The proportions with dose increases and decreases, including new and discontinued medications will be displayed.

Time to Event Analysis

The time will be calculated from RW0 to the first time when:

- The mUFC is above 1.5X the ULN of the central laboratory's reference range; OR
- The mUFC is over 40% above the Baseline (RW0) value if the RW0 value is above the ULN (i.e. >1.0X ULN) for SONICS--completer cohort subjects; OR
- An early rescue criterion is met.

Time from RW0 to first loss of therapeutic response will be defined as the time from the first dose of blinded study drug (levoketoconazole or placebo) to the time when a subject meets one of the criteria above. Time from RW0 to the need for early rescue medication is defined as the time from first dose of blinded study drug (levoketoconazole or placebo)

to the time at which the Investigator withdraws study drug in favor of other treatments including open-label levoketoconazole.

Time to first normalization of mUFC beginning from RW5 (subset of subjects with mUFC above 1.5X ULN at RW5) will be estimated as the time from the first dose of add-on study drug (levoketoconazole or placebo) at RW5 to the time when a subject has confirmed mUFC no more than ULN (i.e. <=ULN) for the assay reference range.

Time to first normalization of LNSC beginning from RW5 (subset of subjects with LNSC above ULN at RW5) will be estimated as the time from the first dose of add-on study drug (levoketoconazole or placebo) at RW5 to the time when a subject has an LNSC result no more than the ULN for the assay reference range.

Each time-to-event endpoint will be analyzed using Kaplan-Meier methods. Median time to each event along with the associated two-sided 95% CI will be presented by treatment group. The time to event distributions will be compared statistically with a two-sided log-rank test. The CI will be regarded as a descriptive statistic.

Normalization of UFC during Dose Titration and Maintenance Phase

The number and proportion of subjects meeting the following criteria will be summarized by therapeutic dose, along with 95% CI for the proportion:

- Achieved normalization of mUFC at the end of Dose Titration and Maintenance Phase (TM7)
- Achieved either normalization of mUFC or partial response (at least 50% decrease in mUFC) at the end of Dose Titration and Maintenance Phase (TM7)

Normalization of LNSC during Restoration Phase

The number and proportion of subjects with normalization of LNSC at RES2 will be analyzed in the same way as the corresponding UFC analyses described in Section 12.5.3.2.

Serum Cortisol and ACTH

Serum cortisol and ACTH are primarily considered to be safety endpoints (see Section 12.5.2.7).

Clinical Signs and Symptoms Excluding Acne, Hirsutism and Peripheral Edema

Individual clinical signs and symptoms, defined in Appendix M, will be summarized by treatment (or dose) group at each time point by number and percent of subjects. For signs and symptoms other than acne, hirsutism and edema, each sign and symptom present at Baseline (RW0) will be graded on a 0 to 3 severity scale (0=absent, 1=mild, 2=moderate, 3=severe, and the severities reported at each visit will be added to derive a total score. Individual sign and symptoms severity scores will also be summarized using

shift tables at each visit. Total severity score and changes from Baseline of the severity total score will be presented by visit.

Other Exploratory Endpoint Analyses

Partial loss of response

Proportions of subjects with partial loss of response (mUFC above normal but no more than 1.5X ULN, or LNSC that was normal at Baseline (RW0) and becomes abnormal (>ULN) based on each of two LNSC collections obtained on different nights) AND clinically significant worsening of signs and symptoms of CS will be compared between groups using a two-sided Fisher's Exact test.

Descriptions of other exploratory analyses will be provided in the SAP.

12.5.4 Pharmacokinetics Analysis

The PK model parameters will include: CL/F, V/F, Ka with associated between subject variability where feasible. Model parameters will be tabulated with associated precision. Derived parameters including t½, AUC and Cmax will be reported, if appropriate. Because the PK of ketoconazole are reported to change over time, time dependent changes in CL/F, AUC, and t½ will be investigated and, if identified, changes will be described in the model. Derived parameters will be tabulated with associated summary statistics.

A population modeling-based approach will be used to evaluate PK data as implemented in NONMEM® (Version 7 level 2 or higher). Subjects with at least one adequately documented dose and concentration record will be considered for inclusion in the population PK evaluation. All evaluations will be conducted based on a pre-specified analysis plan. Standard model building and model evaluation procedures will be followed. Derived parameters will be calculated from the final model. The model will include data derived from the SONICS study.

12.5.5 Pharmacodynamics Analysis

The PD model parameters including UFC Imax, levoketoconazole dose producing UFC IC50, and associated estimates of between-subject variability will be reported. Individual maximal UFC reductions achieved during the TM Phase will be tabulated and summary statistics (mean, median, SD and percent coefficient of variation) will be presented. Stochastic simulations of the expected response for the preferred dose regimen will be generated to explore the range of UFC reduction.

A population modeling-based approach will be used to evaluate PD data (UFC) as implemented in NONMEM® (Version 7 level 2 or higher). Subjects included in the population analysis with at least one adequately documented dose, PK record and UFC record will be considered for inclusion in the population PD evaluation. All evaluations will be conducted based on a pre-specified analysis plan. Standard model building and model evaluation procedures will be followed. Derived parameters such as maximal response will be calculated from the final model as appropriate. The PK-PD models will include data from SONICS.

12.5.6 Subgroup Analyses

Subgroup analyses for the primary endpoint and biomarkers of CS comorbidities endpoints will be performed for a minimum subgroup size of at least 30% of the ITT population. Details will be presented in the SAP.

12.5.6.1 Prior Therapy for Cushing's Syndrome

Subgroup displays for the primary endpoint and the biomarkers of CS comorbidities endpoints will be generated for subjects that enter the study as surgery-naïve versus surgery-experienced. Subgroup analyses by number of prior surgeries, time since last surgery, and category of prior medical treatment will also be explored depending on subgroup size.

12.5.6.2 Prior Radiation Therapy

Subset displays for the primary endpoint and the biomarkers of CS comorbidities endpoint will be generated, excluding subjects who previously received radiation therapy.

12.5.6.3 Hypertensive Subjects

Subgroup displays for the primary endpoint and the biomarkers of CS comorbidities endpoint will be generated for subjects who enter the study while being prescribed antihypertensive medications versus not and subjects who enter the study with a Baseline SBP above 130 mmHg or DBP 90 mmHg or above regardless of antihypertensive medication status versus those with lower blood pressure recordings.

12.5.6.4 Pre-diabetic/Diabetic Subjects

Subgroup displays for the primary endpoint and the biomarkers of CS comorbidities secondary efficacy endpoint will be performed for subjects who enter the study as pre-diabetic (Baseline fasting glucose greater or equal to 100 mg/dL (5.6 mmol/L) and less than 126 mg/dL (7.0 mmol/L) without concomitant use of antihyperglycemic medication) versus those with normal fasting glucose or diabetic (Baseline fasting glucose 126 mg/dL or above or lower fasting glucose while being prescribed antihyperglycemic medications) versus those without diabetes.

12.6 Interim Analyses and Data Monitoring

An interim analysis, also referred to as the End of Randomized Withdrawal Phase analysis, will be conducted after all enrolled subjects have either completed the Randomized Withdrawal Phase or discontinued prior to the end of the Randomized Withdrawal Phase. The interim analysis will include unblinded efficacy and safety data up to the end of the Randomized Withdrawal Phase. Data from the Restoration Phase will not be analyzed. Prior to the unblinding for the interim analysis, the data up to the end of the Randomized Withdrawal Phase will be cleaned and reviewed in a blinded manner to resolve data queries. Details of the planned interim analysis will be provided in the SAP. The SAP will be finalized prior to the unblinding for the interim analysis results.

Subjects, Investigators, study site personnel, representatives of the Sponsor and CRO involved in the monitoring of the study, and representatives of the CRO involved in the

data management of the study will remain blinded at the individual subject level until after the database lock at the end of the study. The names of individuals who will be unblinded at the individual subject level with respect to the interim analysis activities and/or its results will be documented by the statistician who will lead the unblinded team that will conduct the interim analysis.

No changes to the design or conduct of the remainder of the study nor the pre-specified analyses in the SAP will be made based on the interim analysis results. The results from the interim analysis for the primary endpoint and the secondary endpoints during the Randomized Withdrawal Phase will be considered as final. There will be no statistical adjustments of the results at the final analysis that will be conducted after the study ends. Since some of the subjects will still be ongoing in the Restoration Phase at the time of the interim analysis, the results of the final analysis on the secondary endpoints during the Restoration Phase will be analyzed for potential bias resulting from the timing of the interim analysis. These analyses will be described in the SAP.

An independent DSMB will review key safety data at regular intervals throughout the study, as described in Section 12.5.2. The DSMB charter will include details on the restricted access to and the disclosure of the interim safety results presented to the DSMB.

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 Screening) 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 because 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 judgment 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)

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. Such an event might warrant further investigation to characterize and understand it.

AESIs should be reported to the designated safety group as per Section 13.7 regardless of seriousness or causality. Upon receipt, these AEs will be captured in the safety database, targeted follow-up queries will be sent to sites, and source documentation will be sent to the DSMB. As deemed appropriate, analysis of any unscheduled PK samples collected in association with AESIs may be expedited. Once uploaded and reconciled in the clinical database, these results will be forwarded to the DSMB.

The AESIs for this study are defined as follows:

- **Persistent QTc prolongation:** Persistent elevation of the QTc interval is defined as absolute QTc interval above 500 msec (or above 60 msec above the Baseline), with an ECG evaluation on repeat determination continuing to demonstrate QTc prolongation in the absence of plausible alternative explanations. For purposes of comparing the prolonged QTc interval to a Baseline interval for determining if an AESI has occurred, the Baseline interval will be TM0 for events first occurring during the Titration and Maintenance Phase and RW0 for events first occurring during the Randomized Withdrawal Phase or Restoration Phase.
- **Potential hepatic events:** Signs of liver dysfunction or injury, such as:
  - 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** total bilirubin above 2X ULN or INR above 1.5 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;
  - 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 total bilirubin 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 total bilirubin.

Please see Appendix O for guidance on the assessment of abnormal LFTs.

- **Adrenal insufficiency:** A suspicion or diagnosis of adrenal insufficiency, based on the considerations laid out in Section 6.5.3.

13.3 Time Period, Frequency, and Method of Collecting 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?"

All AEs occurring after obtaining the informed consent until the end of the final visit must be reported. All 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. If these have resolved, this should be documented. Changes in intensity or frequency of AEs should be recorded as separate events (i.e., a new record started).

The recording of AEs and SAEs are described in Section 13.4 ("Recording of AEs and SAEs").

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 Adverse Events page(s) of the CRF. 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 alternative causality of event must be recorded in the Adverse Events section of the CRF. AEs believed to be possibly related to study drug must be followed until resolution.

13.5 Evaluating AEs and SAEs

13.5.1 Severity Rating

The severity of AEs and SAEs will be graded per NCI CTCAE, Version 4.0.

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 pre-defined outcomes as described in Section 13.2 "Definition of a SAE".

13.5.2 Relationship to Study Drug

For AEs, 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 adverse event).
- **Unlikely:** There is no reasonable association between the study treatment and the suspected event, and a precipitant of the adverse event 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 AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject. Further information on SAEs will 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 will also be recorded on the "AE" CRF within 24 hours.

13.7 Prompt Reporting of SAEs 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 AESI (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 13.2.2).

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

Reportable Events Contact Details

Email: GlobalSAEInbox@Chiltern.com

24-Hour Call Center Phone: +1 416 568 9804

An SAE Report form must be completed and forwarded via email to Cortendo'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 Cortendo'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 Cortendo's designated safety group will also ensure that the appropriate IRBs/ IECs are notified of the SAE.

14 REFERENCES

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APPENDIX A TIME AND EVENTS SCHEDULES

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

Table 7 Time and Events Schedule for Screening Procedures

	Screening Phase[1]	
Assessments	Subjects who completed SONICS within the previous 6 months and currently receiving levoketoconazole[2],[3]	Levoketoconazole naïve subjects and subjects who completed SONICS > 6 months prior to study entry
Informed Consent	X[4]	X
Eligibility (Inclusion/Exclusion Criteria)	X	X
Medical history and demography	X	X
Prior/concomitant medication [5]	X	X
Physical exam & assessment of appearance		X
Cushing's Signs & Symptoms Form		X
Vital signs (BP and HR in triplicate and temperature)		X
Weight/height/BMI/body habitus		X
HIV / Hepatitis B and C screens		X
ECG – Local ECG machine		(X) [6]
ECG – Spaulding[7]		X
Late night salivary cortisol (2 nights)[8]	X[9]	X
TSH / FT4 and Prolactin		X
Pituitary MRI		X if not within 6 months of TM0 or RW0
FSH and estradiol (women only)		X
Urine βHCG, females		X
Routine clinical laboratory tests (chemistry, hematology, urinalysis)		X
Fasting glucose and insulin measurements		X
INR/PT/PTT		X
HbA1c		X

[1] Screening procedures to be performed following informed consent; Screening Phase for levoketoconazole-naive cohort may last up to approximately 13 weeks to allow prior medication washout before entering the TM Phase (Table 8); Subjects confirmed as eligible for the SONICS-completer cohort will proceed directly to Visit RW0; The Screening Phase, which will rely on data collected during SONICS, will not begin before Visit M12 of SONICS and will end once eligibility is confirmed (the time from confirmation of eligibility and RW0 should be no more than 11 (+3) days); the minimum time requirement is confirmation of the Therapeutic Dose as dictated by tolerability and UFC results). (see Table 9).

[2] If there is a time gap between completion of Screening and TM0 or RW0 for subjects currently receiving levoketoconazole, then open-label levoketoconazole should be continued between Screening and TM0 or RW0 to maintain the Therapeutic Dose. If rolling over from SONICS, subjects will be dispensed LOGICS medication starting at the screening visit. If entering from EAP, subjects will stay on open-label levoketoconazole dispensed from EAP until the Baseline visit.

[3] For subjects who have completed SONICS more than 6 months prior to the Screening Phase and have not been on a stable Therapeutic Dose throughout the previous 12-week period, Screening Procedures will mimic those for the levoketoconazole-naïve subjects to confirm eligibility for the current study.

[4] Informed consent for subjects who completed SONICS is administered at or prior to the Screening visit prior to randomization or performance of any study procedures for this protocol.

[5] Blood pressure, diabetes, cholesterol, anti-inflammatory, and CS-specific medications will be captured separately from other medications.

[6] Local machine to be used only when Spaulding device is non-operational. Local ECGs must be transmitted to Spaulding for central reading via printout.

[7] Spaulding ECGs will be obtained over a minimum of 1 minute up to a maximum of 5 minutes at Screening.

[8] Ideally, UFC and LNSC samples should be collected before DST. If collecting UFC and LNSC samples after administering dexamethasone, do not collect the LNSC until at least 5 days after dexamethasone is administered; do not start collection of the UFCs until at least 14 days after dexamethasone is administered (see Section 6.4.5.3).

[9] Subjects rolling over from SONICS at the M12 visit (and after signing the informed consent form for LOGICS) will need one additional LNSC collection for LOGICS screening (total of 2 collections).

	Screening Phase[1]	
Assessments	Subjects who completed SONICS within the previous 6 months and currently receiving levoketoconazole[2,3]	Levoketoconazole naïve subjects and subjects who completed SONICS > 6 months prior to study entry
OGTT[10]		X
Dexamethasone Suppression Test (DST)[11]		X if not done within previous 60 days[12]
ACTH		X
Fasting lipid measurements, triglycerides		X
Spot urine for albumin/creatinine ratio		X
Dispense study medication/diary	X[13]	X[14]
Testosterone, free/total		X
Adverse Event assessment[15]	X	X
24-h UFC/free cortisol/creatinine/ urinary volume (3 collections)	X[16]	X

[10] OGTT should only be performed in subjects with IFG (i.e. fasting glucose ≥ 100 mg/dL (5.6 mmol/L) and < 126 mg/dL (7.0 mmol/L)) who do not have diabetes and who are not receiving medications to lower blood glucose (i.e. antihyperglycemics).
[11] DST is not needed at screening for subjects currently receiving levoketoconazole at screening.
[12] This procedure will necessitate a second visit that can be performed at home by a qualified HHC professional.
[13] If rolling over from SONICS, subjects will return SONICS medications and will be dispensed LOGICS medication starting at the screening visit. If entering from EAP, subjects will stay on open-label levoketoconazole dispensed from EAP until the Baseline visit.
[14] Only the study diary should be dispensed at Screening (and not study medication) for levoketoconazole-naïve subjects and subjects currently receiving levoketoconazole via an EAP but who completed SONICS greater than 6 months ago.
[15] AEs at Screening will only include AEs reported after ICF signing. AEs reported in SONICS protocol and present at Screening will be recorded as medical history.
[16] Subjects who completed SONICS at M12 visit (and after the informed consent form for LOGICS is signed) will need one additional UFC collected at Screening (total of 3 UFC collections needed).
NOTE: The UFC samples should not be collected within 2 weeks (approximately 14 days) after administering DST.

Table 8 Time and Events Schedule for Dose Titration and Maintenance Phase (levoketoconazole-naïve Cohort)

Assessments	Dose Titration and Maintenance (TM) Phase [1]									
	BL	*Visit interval 14 days (± 3)*							**Additional safety visit (in office)[2]**	**Additional safety visit (HHC)[2]**
	TM0[3]	**TM1**	**TM2**	**TM3**	**TM4**	**TM5**	**TM6**	**TM7[4]**		
Prior/concomitant medication[5]	X	X	X	X	X	X	X	X	X	X
Administer Study drug/patient study diary review	X	X	X	X	X	X	X	X	X	X
Drug accountability/dispensation of drug and study diary	X	X	X	X	X	X	X	X		
Physical exam & assessment of appearance	(X)			X		X		X		
Cushing's Signs & Symptoms Form	(X)	X	X	X	X	X	X	X		
Vital signs (BP and HR in triplicate and temperature)	(X)	X	X	X	X	X	X	X	X	X
Weight/height/BMI/body habitus	(X)				X			X		
Abdominal Girth (in triplicate)	X				X			X		
ECG – Local ECG machine[6]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	
ECG – Spaulding[7]	X	X	X	X	X	X	X	X	X	X
Late night salivary cortisol (1 night)[8]		X	X	X	X	X	X			
Late night salivary cortisol (2 nights)[8]	(X)[8]							X		
TSH / FT4 and Prolactin	(X)[9]							X		
Urine βHCG, females	X	X	X	X	X	X	X	X		
Routine clinical laboratory tests (chemistry, hematology, coagulation, urinalysis)	(X)	X	X	X	X	X	X	X	X	X
Fasting glucose and insulin measurements	(X)	X	X	X	X	X	X	X	X	X
HbA1c	X							X		

[1] The approximate usual interval between dose-titration visits will be 14 days (±3 days) [including reporting time for UFC levels and safety laboratory assessments].
[2] One extra safety evaluation 5 (±2) days after each dose escalation to 750 mg/day or above during the TM phase to include: AEs, vital signs, routine safety, laboratory assessments (including liver safety tests), ECGs, morning serum cortisol. PK sampling at TM3, TM4, TM5, and TM6 could alternately be performed during additional safety visit required for DL4, DL5, DL6 and DL7 if required. Additional safety visit can occur anytime bases on dose escalations to 750 mg/day or above. Safety visit can be performed at home by a qualified HHC professional.
[3] TM0 serves as Baseline for the TM Phase. Screening procedures completed within 3 weeks of TM0 (within 2 weeks for LNSC, QTc interval and liver safety tests; and within 6 weeks for UFCs) will be used as the TM0 or Baseline value. If other Screening procedures were completed more than 3 weeks prior to TM0, then they will be repeated at TM0, except for pituitary MRI, which may be completed up to 6 months prior to TM0 or RW0 and UFCs which may be completed up to 6 weeks prior to TM0. All blood samples, except for post-dose PK samples, should be obtained prior to administering the first dose of levoketoconazole.
[4] TM7 procedures will also be completed by subjects who prematurely withdraw from the study during the TM Phase.
[5] Blood pressure, diabetes, cholesterol, anti-inflammatory, and CS-specific medications will be captured with other medications but will require specification of these medication types.
[6] Local machine to be used only when Spaulding device is non-operational. Local ECGs must be transmitted to Spaulding for central reading via printout.
[7] Spaulding ECGs will be obtained over a minimum of 1 minute up to a maximum of 5 minutes and within approximately 1-2 h after drug administration at each visit.
[8] LNSC collections should be collected before each visit. LNSC collections during Screening to provide the Baseline measurements should be collected within 14 days prior to dosing at TM0.
[9] TSH/FT4 and prolactin to be measured if not done at Screening.

Assessments	Dose Titration and Maintenance (TM) Phase [1]									
	BL	*Visit interval 14 days (± 3)*							**Additional safety visit (in office)[2]**	**Additional safety visit (HHC)[2]**
	TM0[3]	**TM1**	**TM2**	**TM3**	**TM4**	**TM5**	**TM6**	**TM7[4]**		
OGTT (pre-diabetic subjects with IFG only)[10]						X		X		
Serum cortisol (morning)	X	X	X	X	X	X	X	X	X	X
ACTH	(X)			X		X		X		
Fasting lipid measurements, triglycerides	(X)				X			X		
hsCRP	X				X			X		
Spot urine for albumin/creatinine ratio (only if abnormal at Screening)	(X)			X			X	X		
Testosterone, free/total	(X)			X		X		X		
Safety contact[11]	X	(X)	(X)							
Adverse Event assessment	X	X	X	X	X	X	X	X	X	X
Cushing QoL questionnaire	X							X		
BDI-II instrument	X							X		
24-h UFC/creatinine/ urinary volume (3 collections)[12]	(X)							X		
24-h UFC/creatinine/ urinary volume (2 to 3 collections)[13]		X	X	X	X	X	X			
Pharmacokinetic sampling[14]	X		(X)	(X)	(X)	(X)	(X)	X	(X)	(X)

[10] Levoketoconazole-naïve cohort subjects with IFG should have OGTT prior to RW0 if still escalating at TM5 after the Therapeutic Dose has been established in TM Phase (i.e. at TM7).
[11] Contact (method by subject preference) approximately 1 week after first dose and each dose adjustment up to DL3.
[12] Prior to the final open-label visit (TM7), **three** complete 24-hour urine specimens will again be obtained (NOTE: collections should be collected prior to the visit and need not be repeated if the final open-label visit coincides with the initial establishment of UFC normalization) to confirm maintenance of UFC normalization prior to randomization, denoting UFC-eligibility for the Randomized Withdrawal Phase. UFC results must be received before next TM visit in order to determine the need to escalate dose.
[13] First 24-hour urine collection will be ~Day 8 (±2 days) and the second collection will be ~Day 9 (±2 days) after start of each dose level. 24-hour UFC collections should occur prior to and not at the visit and results must be received before next TM visit. If UFC ≤ULN, there will be an additional 24-hour urine collection to confirm UFC results.
[14] During the TM Phase, PK samples should be drawn pre-dose, at 1.5-2.5 hours after dosing at TM0 and TM7 and at approximately 6-8 hours after dosing at one interim visit (TM2-TM6 or an additional safety visit) of the subject's choosing. The subject should forgo taking study medication on the day of the scheduled visit, so that dosing can be done at the clinic or by HHC professional. The 6-8-hour time point for PK sampling is non-optional. In case of AESI, a PK sample should be obtained as close to the time of the event as possible.

Table 9 Study Time and Events Schedule for Randomized Withdrawal Phase and Restoration Phase (Both Cohorts)

Assessments	Randomized Withdrawal Phase [1]						Restoration Phase	
	BL	D10	D20	D30	D40	D58	*Visit interval 28 days (± 5)*	
	RW0 [2]	RW1	RW2	RW3	RW4	RW5 [3]	RES1	RES2 [4]
Concomitant medication [5]	X	X	X	X	X	X	X	X
Administer study drug/patient diary review and dispensation	X	X	X	X	X	X	X	(X) [6]
Drug accountability/dispensation of drug [7]	X	X	X	X	X	X	X	X
Physical exam & assessment of appearance	X			X		X		X
Cushing's Signs & Symptoms Form	X	X	X	X	X	X	X	X
Vital signs (BP and HR in triplicate and temperature)	X	X	X	X	X	X	X	X
Weight/height/BMI/body habitus	X			X		X		X
Abdominal Girth (in triplicate)	X					X		X
ECG – Local ECG machine [8]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
ECG – Spaulding [9]	X	X	X	X	X	X	X	X
Safety contact (between visits) [10]							weekly	

[1] Visits RW1, RW2 and RW4 are required but are optionally **at-home visits** for which assessments may be made by a qualified HHC professional appointed by the Sponsor and agreed to with the Investigator and subject. For RW1, RW2 and RW4, the visit can be up to 2 days before D10, D20 and D40, respectively. For RW3 and RW5, the visit can be up to 4 days before D30 and D58, respectively.

[2] RW0 serves as the Baseline Visit for the primary efficacy endpoint for all subjects. The procedures done at Visits TM7 (for levoketoconazole-naïve cohort), at Screening (for subjects who have exited SONICS more than 6 months prior to the Screening Phase and have been on a stable Therapeutic Dose throughout the previous 12-week period), or at SONICS Visit M12 (for subjects who completed SONICS) **need not be repeated** at RW0 unless a dose change was required at Visit TM7; however, the findings/assessments from those procedures will be entered into the clinical database at Visit RW0 for subjects continuing into the Randomized Withdrawal Phase, and Eligibility must be confirmed for all subjects at RW0 to include confirmation of continuous therapy with a Therapeutic Dose of levoketoconazole for the requisite time period prior to RW0. RW0 should be scheduled to occur no earlier than 14 weeks and no later than ~19 weeks after TM0, depending on duration until reaching a Therapeutic Dose. At least 4 weeks should elapse between reaching the Therapeutic Dose and RW0 to ensure tolerability and stability (continued effectiveness) of the Therapeutic Dose. Randomization (RW0) may occur concurrently with the final TM Phase visit or no more than 11 (+3) days later unless a dose change was required at Visit TM7.

[3] Subjects who require early rescue with open-label levoketoconazole will undergo RW5 procedures immediately prior to administration of open-label rescue medication (except ECG to be done 1-2 hours after administration of rescue medication). Subjects who complete all Randomized Withdrawal visits will undergo RW5 procedures immediately prior to administration of blinded Restoration Phase study medication (except ECG to be done 1-2 hours after administration of rescue medication). As this is open-label treatment, titration beyond the previously established Therapeutic Dose is permitted if medically necessary. The visit interval between RW5 and RES1 is 28 (±5) days

[4] RES2 procedures will also be performed by subjects who prematurely withdraw from the study during Restoration Phase.

[5] Blood pressure, diabetes, cholesterol, anti-inflammatory, and CS-specific medications will be captured as specific categories on the eCRF.

[6] Accountability check only. Drug administration will not occur in conjunction with this study at RES2.

[7] Drug accountability and dispensation only to be completed when visits are performed in-clinic and not applicable to HHC visits. No dispensation of drug to occur at RW1, RW2, RW4 and RES2. All drug-dispensation visits including any unscheduled visit for distribution of drug should be recorded in the IRT.

[8] Local ECG machine to be used only when Spaulding device is non-operational. Local ECGs must be transmitted to Spaulding for central reading via printout.

[9] Spaulding ECGs will be obtained over a minimum of 1 minute up to a maximum of 5 minutes at Screening and within approximately 1 – 2 h after drug administration at each visit.

[10] Weekly safety contact during Restoration Phase (between RW5 and RES2) —method according to preference—to be made between visits to inquire regarding adverse events, subject status and to ensure compliance with study medication.

Assessments	Randomized Withdrawal Phase [1]						Restoration Phase	
	BL	**D10**	**D20**	**D30**	**D40**	**D58**	*Visit interval 28 days (± 5)*	
	RW0 [2]	**RW1**	**RW2**	**RW3**	**RW4**	**RW5** [3]	**RES1**	**RES2** [4]
Late night salivary cortisol (1 night) [11]		X	X	X	X		X	
Late night salivary cortisol (2 nights)[11]	X					X		X
TSH / FT4 and Prolactin [12]	X					X		X
Pituitary MRI[13]	X					X		
Urine βHCG, females	X	X	X	X	X	X	X	X
Routine clinical laboratory tests (chemistry, hematology, coagulation, urinalysis)	X	X	X	X	X	X	X	X
Fasting glucose and insulin measurements	X	X	X	X	X	X	X	X
HbA1c	X					X		X
OGTT (pre-diabetic subjects with IFG only)	(X) [14]					X		X
Serum cortisol (morning)	X	X	X	X	X	X	X	X
ACTH	X	X	X	X	X	X	X	X
Fasting lipid measurements, triglycerides	X					X		X
hsCRP	X					X		X
Spot urine for albumin/creatinine ratio (only if abnormal at Screening)	X					X		X
Testosterone, free/total	X					X		X
Adverse Event assessment	X	X	X	X	X	X	X	X
Cushing QoL questionnaire	X					X		X
BDI-II instrument	X					X		X
24-h UFC/creatinine/ urinary volume (3 or 4 collections)[15]	X					X		X[16]
24-h UFC/creatinine/ urinary volume (2 collections)[15]							X[16]	
24-h UFC/creatinine/ urinary volume (2 to 3 collections) [15,17]		X	X	X	X			

[11] LNSC collections must be collected before the visit. A second night's collection should be done if LNSC is being used to establish the need for early rescue therapy during Randomized Withdrawal Phase.

[12] TSH/FT4 to be measured at TM7 Visit during the TM Phase. If subjects reach their maximum dose before the TM7 visit during the TM Phase, they will have TSH/FT4 measured at Visit RW0 of the Randomized Withdrawal Phase.

[13] SONICS-completer cohort subjects will have Pituitary MRI done as part of SONICS Visit M12. The Visit RW0 and RW5 MRI may be performed up to 2 weeks BEFORE the visit.

[14] For those who completed SONICS and are pre-diabetic with IFG at the SONICS baseline should have OGTT done to become the Baseline value for current study. Levoketoconazole-naïve subjects should have the test completed during the screening phase and prior to RW0 after the Therapeutic Dose has been established in the TM Phase (i.e. at TM7).

[15] 24-hour UFC collections should occur prior to the visit.

[16] For the urine collection between RW5 and RES1, subjects should have received the previously achieved Therapeutic dose of blinded study medication for at least 1 week before collections commence and complete and at least 1 week before the RES1 visit. For urine collections between RES1 and RES2, urine collection should commence at approximately Day 18 of the Restoration Phase.

[17] First 24-hour urine collection will be ~Day 8 (±2 days) and the second collection will be ~Day 9 (±2 days) after the clinic visit. A third UFC collection should be done if UFC is being used to establish the need for early rescue therapy during the Randomized Withdrawal Phase.

Assessments	Randomized Withdrawal Phase [1]						Restoration Phase	
	BL	**D10**	**D20**	**D30**	**D40**	**D58**	*Visit interval 28 days (± 5)*	
	RW0 [2]	**RW1**	**RW2**	**RW3**	**RW4**	**RW5** [3]	**RES1**	**RES2** [4]
Pharmacokinetic sampling[18]							X	

[18] During the Restoration Phase, PK samples should be drawn pre-dose and between 1.5 to 2.5 hours after dosing only at RES1. In case of AESI, a PK sample should be obtained as close to the time of the event as possible.

APPENDIX B LABORATORY ANALYTES

Laboratory studies to be collected as per Time and Events Schedules (Appendix A).

Disease-related Assessments

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

Salivary cortisol

Serum cortisol

Plasma ACTH

Dexamethasone

CS Cardiovascular Co-Morbidity Biomarkers

Fasting glucose

Fasting insulin

Hemoglobin A1c [HbA1c]

High-sensitivity C-reactive protein [hsCRP]

Fasting lipids and triglycerides: including total cholesterol, high density lipoprotein cholesterol [HDL-C], and low density lipoprotein-cholesterol [LDL-C]

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	***Liver Safety Tests***
Creatinine	AST (SGOT)
Sodium	ALT (SGPT)
Potassium	GGT
Chloride	Alkaline phosphatase
Total CO_2	Total and direct bilirubin
Calcium, Magnesium, Phosphate	Coagulation tests (INR/PT/PTT)
Uric Acid	LDH
Albumin	
Total Protein	

Urinalysis

Specific gravity
pH, glucose, protein, blood and ketones by dipstick
Microscopic examination (if blood or protein is > trace positive by dipstick)

Other analytes/measures

HIV

Hepatitis B and C antibodies

Free and total testosterone (both men and women)

Estradiol and FSH (women only)

Pregnancy test (urine βHCG, all women regardless of childbearing potential)

Spot urine for albumin/creatinine ratio—if normal at Baseline, no further testing is required throughout the study

TSH/free T4, Prolactin

OGTT (pre-diabetic subjects with IFG only)

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 CRFs 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 CRFs 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 (2) years following the date 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 (2) years after the investigation is discontinued and the 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 CRFs 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 and 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 (HIPAA) and applicable data protection regulations in the countries concerned.

Institutional Review/Ethical Review

The protocol and informed consent form 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 situation, 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 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 informed consent forms. 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, Study Management and Materials).

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, with rights of final authorship decisions to be held by Cortendo, unless superseded by an agreement stipulating otherwise. Factors determining merit will include active participation in study design and conduct, as well as interest and ability to participate meaningfully in analyzing or interpreting, writing or presenting study results. 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 participating in multicenter studies 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 CONDITIONS ASSOCIATED WITH PSEUDO-CUSHING'S SYNDROME

Reference: Nieman 2008. 48-hour, 2 mg dexamethasone suppression test may be necessary to exclude pseudo-Cushing's disease.

Some clinical features of CS may be present:

- Pregnancy
- Depression and other psychiatric conditions
- Alcohol dependence
- Morbid obesity
- Poorly controlled diabetes mellitus
- Polycystic Ovary Disease (PCOD)

Unlikely to have any clinical features of CS

- Physical stress (hospitalization, surgery, pain)
- Malnutrition, anorexia nervosa
- Glucocorticoid resistance
- Intense chronic exercise
- Hypothalamic amenorrhea
- Cortisol-binding globulin (CBG) excess (increased serum but not urine cortisol)

APPENDIX H 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 (ADA) standards for the diagnosis of prediabetes consider three different categories of prediabetes, based on measures of 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 (IFG), as follows:

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

ADA criteria for the diagnosis of diabetes will be used as follows.

Diabetes Is Diagnosed by One of the Following Criteria:

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

OR

- 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

- 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

- HbA1C ≥ 6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay.

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

APPENDIX I 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 10 Blood Pressure Classification (for Adults Over 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 11 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. > 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 J CONCOMITANT MEDICATIONS PROHIBITED OR TO BE USED ONLY WITH PRIOR PERMISSION

Table 12 through Table 20 provide examples of drugs that are **PROHIBITED** for concomitant use in COR-2017-01. Table 21 through Table 23 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 rather than as a comprehensive set.

Prohibited concomitant medications

Table 12 Steroidogenesis Inhibitors and Systemic Corticosteroids

Interferes with study drug assessment; must be avoided or washed out prior to Baseline Assessments, including UFCs and LNSCs

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 13 Dopamine Agonists

Interferes 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 14 Synthetic Progestins that Bind with Moderate to High Affinity[1] to Glucocorticoid Receptor (GR) or Mineralocorticoid Receptor (MR)

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

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

Table 15 Somatostatin Analogs

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

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

Table 16 Weight Loss Medications

Interferes with endpoints assessment; must be avoided or washed out

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

Table 17 Drugs Predicted to Interfere with Levoketoconazole Absorption

Must be avoided; use an allowed substitute or wash out

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

[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.

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 18).
- 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 19).

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 judgment of the Medical Monitor or delegate:
https://mor.nlm.nih.gov/RxNav/search?searchBy=String&searchTerm=ketoconazole

Table 18 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 19 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 20 Drugs that can Cause QTc Prolongation

Must be avoided. Permission prior to use is required unless no suitable alternative is available after the Baseline Visit

Alfuzosin	Eliglustat	Perphenazine
Amiodarone	Erithromycin	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
Dolasetron	Mirtazapine	Tolterodine
Disopyramide	Moexipril/HCTZ	Toremifene
Domperidone	Moxifloxacin	Trimipramine
Donepezil	Norfloxacin	Tropisetron
Dosulepin	Nortriptyline	Vardenafil
Doxepin	Ofloxacin	Venlafaxine
Dronedarone	Ondansetron	Ziprasidone
Droperidol	Paliperidone	Zuclopenthixol

Medications that require prior permission to be used concomitantly with study drug

Table 21 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 22 Topical or Inhaled Steroids

Interferes 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	Traimcinolone acetonide

Table 23 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 K SIGNS AND SYMPTOMS OF CONDITIONS FOR RISK MANAGEMENT PURPOSES

Disease	Symptoms	Signs	Laboratory values
Adrenal Insufficiency	Fatigue/Tiredness/Malaise Weakness Anorexia Nausea Vomiting Constipation Abdominal pain Diarrhea Headache Salt carving Arthralgias/Myalgias Dizziness (esp. on standing) **Less common:** Irritability Depression Sweating Fever	Weight loss Hypotension Hyperpigmentation **Less common:** Hypoglycemia	Serum cortisol level < 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 L QUALITY OF LIFE QUESTIONNAIRE

CUSHING'S SYNDROME QUALITY OF LIFE QUESTIONNAIRE

(CushingQoL)

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 M 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 or qualified trained HHC professional

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*

7. Acne

Grading System for 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	Left Cheek	Chin
Right Cheek	Nose	Chest and Upper Back

Grading Scale:

0 = No Lesions
1 = ≥ one comedone
2 = ≥ one papule
3 = ≥ one pustule
4 = ≥ one nodule

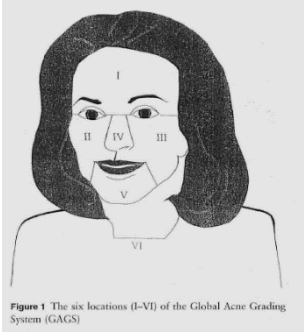

Figure 1 The six locations (I–VI) of the Global Acne Grading System (GAGS)

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)	

8. 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	Abdominal	Thigh
Chin	Pubic	Back
Chest	Arm	Buttocks

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

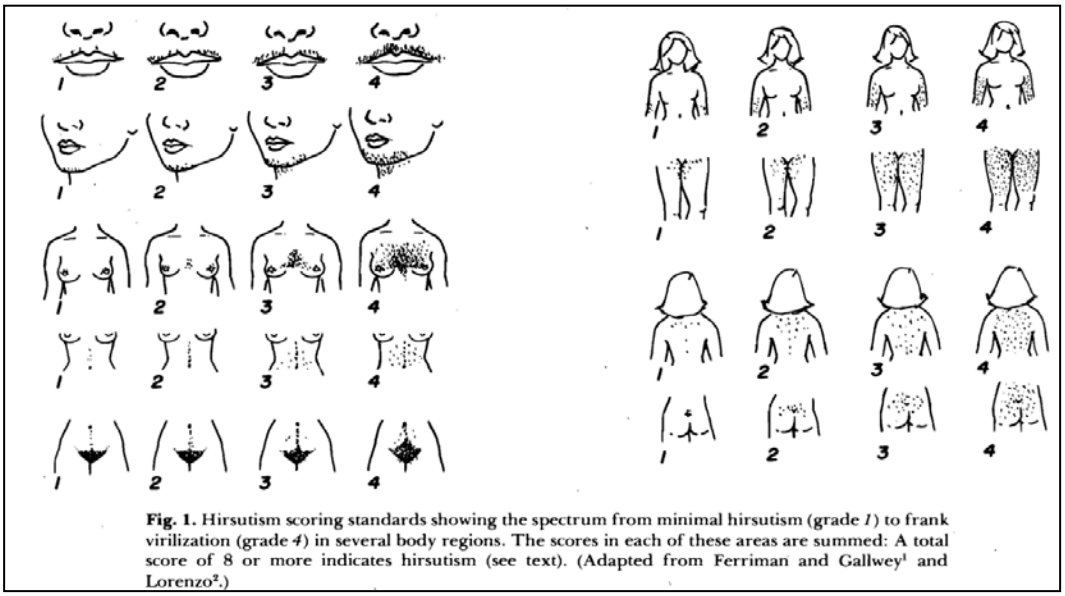

Fig. 1. Hirsutism scoring standards showing the spectrum from minimal hirsutism (grade *1*) to frank virilization (grade *4*) in several body regions. The scores in each of these areas are summed: A total score of 8 or more indicates hirsutism (see text). (Adapted from Ferriman and Gallwey[1] and Lorenzo[2].)

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	

9. Peripheral edema

Edema will be assessed according to the method established by Brodovicz 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.

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

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		

Name of Assessor (PI or designated site personnel) or qualified trained HHC professional completing assessment:

(Printed)_____

Signature of Assessor (PI or designated site personnel) or qualified trained HHC professional completing assessment:

_____

Date_____

APPENDIX N 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

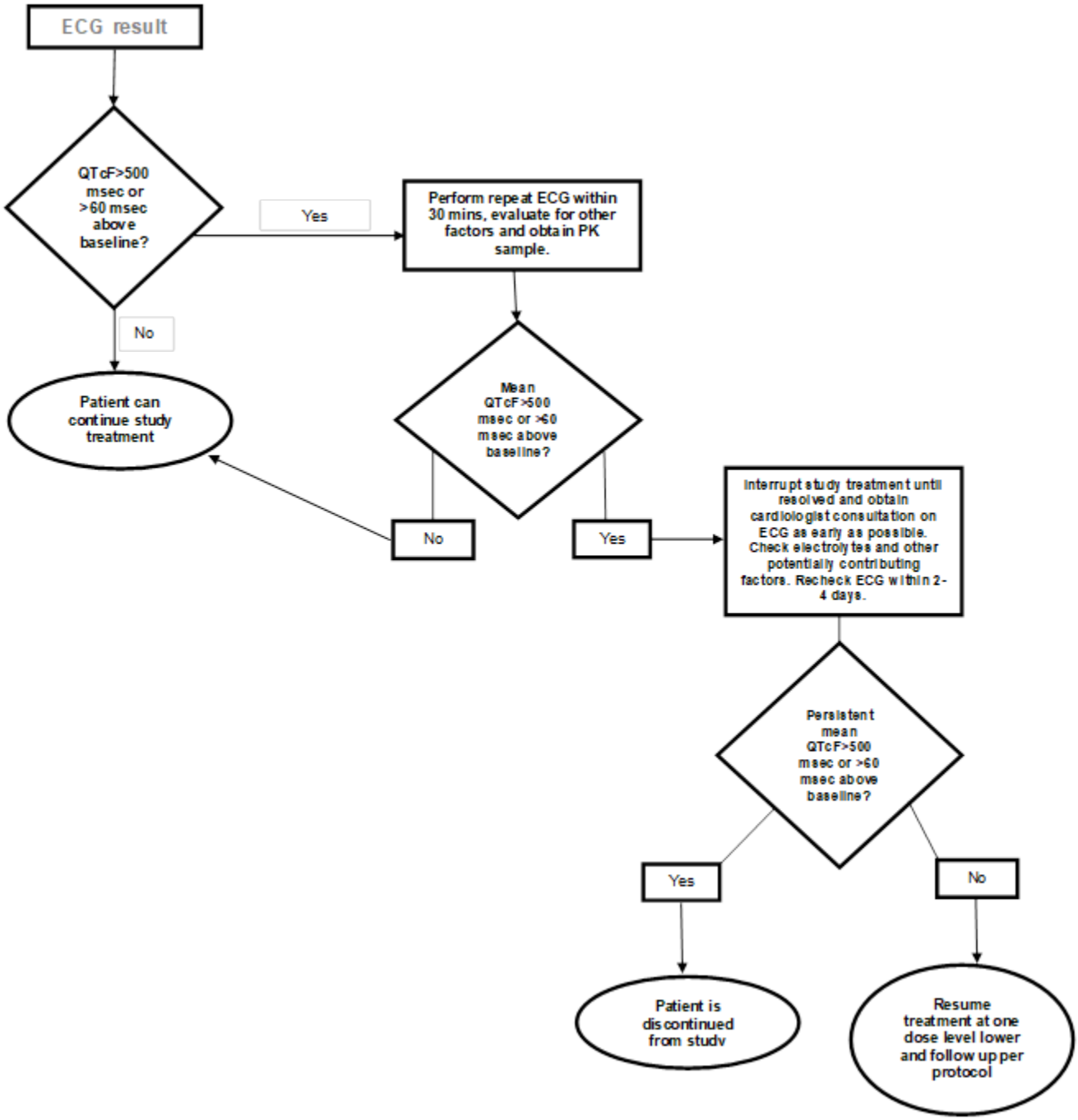
_____ Subtotal Page 1

_____ Total Score

BDI-II F9542DFRM-A

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

Additional information for evaluation and management of prolonged QTc Interval



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 liver function tests), 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/pruritus

   Eosinophilia

   Dark urine

   Acholic stool

   Fever

   Right upper quadrant pain/tenderness
6. Information regarding liver specialist consultation.
7. Results of any liver function tests performed to date (including baseline and repeat testing).
8. All INR, PT and PTT readings (including baseline).
9. Imaging procedures.
10. Any other tests performed (liver panel below can be ordered from central laboratory).

HEPATITIS A ANTIBODY, IgM (Focus)

HEPATITIS B CORE IGM AB (Centaur)

Hepatitis B Virus DNA Quant PCR (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

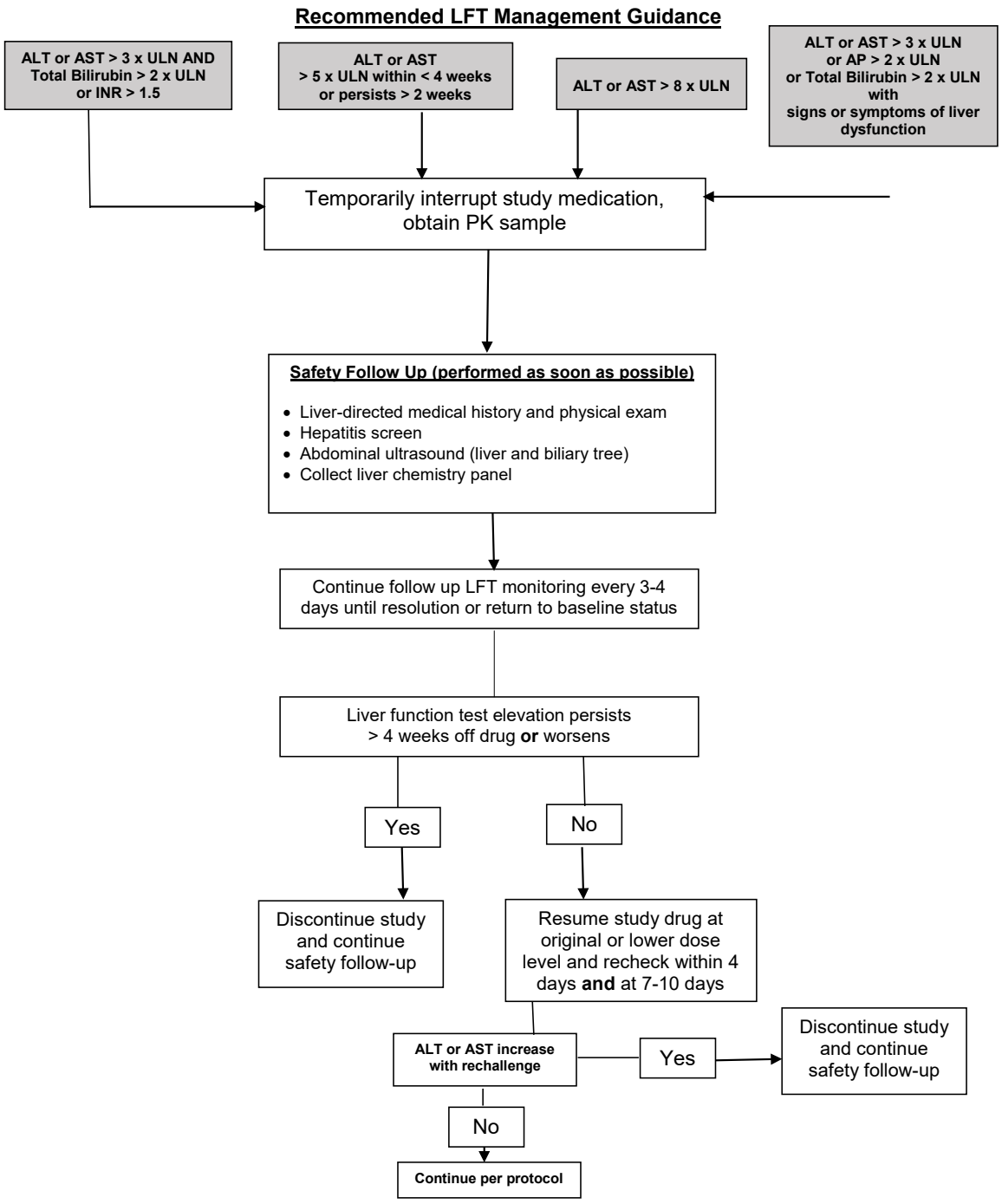
ANA screen with reflex to titer and pattern (Panel)-Bioplex

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 or INR > 1.5
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 Total Bilirubin > 2 x ULN with signs or symptoms of liver dysfunction
Temporarily interrupt study medication, obtain PK sample
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
Resume study drug at original or lower dose level and recheck within 4 days and at 7-10 days
ALT or AST increase with rechallenge
Yes
Discontinue study and continue safety follow-up
No
Continue per protocol

Recommended for Management of Adrenal Insufficiency