CORTENDO

CLINICAL STUDY PROTOCOL

An Open Label Study to Assess the Safety and Efficacy of COR-003 (2S, 4R-Ketoconazole) in the Treatment of Endogenous Cushing's Syndrome

Protocol Number	COR-2012-01
Compound	COR-003
IND No.	115968
EudraCT No.	2013-002133-37
Phase	3
Dates:	
Amendment 6	25 October 2016
Amendment 5	16 April 2015
Amendment 4	28 August 2014
Amendment 3	26 February 2014
Amendment 2	20 October 2013
Amendment 1	09 September 2013
Original	10 April 2013
Sponsor	Cortendo AB 900 Northbrook Drive, Suite 200 Trevose, Pennsylvania, 19053 USA Cortendo AB c/o TMF Sweden AB Sergels Torg 12 111 57 Stockholm Sweden

Revision Chronology

10 April 2013	Original
09 September 2013	Amendment 1: • Updated/clarified inclusion/exclusion criteria for the following: prior irradiation, candidates for surgery, subjects with Cushing's disease, prior treatment, history of prolonged QT syndrome, LFT thresholds, history of alcohol/drug use, concomitant medications. • Included analysis criteria for missing data to analyze restricted last observation carried over (RLOCF) and deleted modified ITT (mITT). • Clarified criteria for prolonged QTc observations and added more ECG assessments for subjects on doses >600 mg/day. • Updated Time and Events Table. • Editorial changes for clarity and consistency.
20 October 2013	Amendment 2: • Deleted upper end for BMI in Exclusion Criteria. • Late night salivary cortisol to be conducted in triplicate at certain time points. • Addition of ambulatory blood pressure monitoring based on feasibility.
17 February 2014	Amendment 3: • The PK sampling scheme now refers to planned sequences, instead of dose levels, including an explanation of the sample collection plan. • Use of acetaminophen >3 g/day was added to exclusion criteria and list of prohibited medications. • Pregnancy is no longer considered an SAE. • Subjects to complete diary cards for medication administration to measure compliance. • Dexamethasone suppression test to be conducted at 12 months in the Extension Phase. • Dose Titration determined based on UFC results only and not serum cortisol levels.

	• Ambulatory blood pressure to be evaluated throughout the study and formally analyzed. • Microalbuminuria assessments to be determined during Maintenance Phase ONLY if abnormal at Baseline. • Editorial changes for clarity and consistency.
28 August 2014	Amendment 4: • Medical Monitor and Sponsor signatory changed to Anthony DelConte, MD. • Description of DSMB responsibilities, including the use and role of an adjudication committee, was removed from the protocol, because those are defined in the DSMB charter. • The approximate time between dose adjustments was changed to 15 (±7) days from 15 (±2) days. • Inclusion Criterion #6 clarified to indicate that CS subjects with or without radiographically visible adenomas may be enrolled. • Exclusion Criterion #10 revised to provide more detail regarding contraceptive usage. • Exclusion Criterion #14 revised to allow screening assessments to occur following informed consent signature and discontinuation of prohibited medication(s). • Exclusion Criterion #15 clarified regarding diabetic subjects requiring hospitalization. • Screening Phase duration was changed to ~12 weeks from 8. • Diabetic subjects will be allowed a small snack if intolerant of fasting when required for laboratory or ECG assessments. • Added new section: “Medications to be used with Caution”, which includes list of medications mainly mediated by CYP3A4. This information was previously included as part of prohibited medication. • Revised Time and Events Table for further transparency. • Editorial changes for clarity and consistency.

16-April-2015	Amendment 5 • Removal of assessment of ambulatory blood pressure • Late night salivary cortisol samples will be measured over 2 nights instead of 3 nights, where applicable • The number of pharmacokinetic collection samples have been decreased as follows: o samples will be collected at 1.5 h and 2.5 h post dose during at least 2 visits at different dose levels from all subjects o a third sample will be collected between 6 to 8h post dose in a subset of 10 to 15 subjects • The Targeted Signs and Symptom of Clinical Interest Form was revised and renamed "Assessment of Clinical Signs and Symptoms of Cushing's Syndrome" • Added the Beck Depression Inventory (BDI-II) instrument to be administered at the same time as the Cushing's QoL questionnaire • The Visual Analog Questionnaires for Physicians and Subjects was removed • Option for TID dosing was removed • Added a section on AEs of special interest and their analyses was included in secondary objectives • Added details on acceptable forms of contraception for men and women of childbearing potential • Objectives and endpoints were stated more precisely; Secondary Objectives were newly ordered and reworded for clarification; distinction between secondary and exploratory endpoints; clarification of "metabolic endpoints" to be changes in the biomarkers of CS comorbidities (diabetes, hypertension, hypercholesterolemia and obesity); a new exploratory composite endpoint of "Clinical benefit" was introduced; corresponding changes in the data analyses • Overall change in organization of the protocol and modifications to all sections of the protocol for clarity

25-October-2016	Amendment 6 • Update Sponsor Approver information on Sponsor Approval Page. • Clarified and aligned the primary, secondary and exploratory objectives and endpoints (Section 2 and Section 3) • Clarified the pharmacokinetic and pharmacodynamics objectives and endpoints by moving them into a new section (Section 2.4 and Section 3.4) • Added clarification to primary endpoint (Section 3.1) and the analysis (Section 12.5.2.1) to align with the primary objective to evaluate the range of effective doses. • Separated details about Screening Period and inserted a new section (Section 4.1). • Guidance regarding the option to re-screen subjects that have had a change in their medical condition that would increase their likelihood of eligibility for participation was added to new Section 4.1 and to Section 6. • The interval between dose level visits (if additional 24-hour urinary cortisol collections are not required) was clarified to be approximately 18 days (±4 days) in Section 4.2. • The collection of two adequate 24-hour urine specimens during the titration phase (Section 4.2.1) has been clarified to start collections on Day 10 (±1 day) after the start of each dose level, ideally on two consecutive days. • Section 4, Section 11.1, and Appendix A updated to include references to the expanded access program availability and the timing of the preparatory procedures, which might occur during their visits for COR-2012-01. • Information about the option to receive continued treatment through the expanded access protocol (COR-2015-EAP), where available, was added to Section 4, Section 4.5, and Section 4.7. Subjects participating in expanded access do not need to complete the Follow-Up Visit for COR-2012-01, as they will be continuing treatment with COR-003.

	• Section 4.2.2 and Appendix A clarified timing for additional safety visits to 1 safety visit occurring 7 (±3) days following each Dose Level titration. • Inserted new heading for the Dose Titration Phase (Section 4.2) and updated subheadings. • Wording in new Section 4.2 to specify timing and testing requirements for subjects through the Dose Titration Phase and to determine when to transition subjects to the Maintenance Phase. Timing and window for the visit after the two confirmatory 24-hour urine samples has been increased to 30 days (±7 days) for logistical reasons. • Included a footnote to Table 1 in new Section 4.2.1 and added Section 8.2.1 to specifically address dosage decreases to DL0. • The timing for additional safety visits for doses >600 mg total daily dose has been clarified with visit windows in Section 4.2.2. • Section 4.2.2 and Section 6.2.7.1 updated with additional safety monitoring to include ECG testing. • In Section 4.3 (previously Section 4.2) the timings for Maintenance Visits, to include visit windows, was added (every 30 days ± 7 days); clarification of documentation for dose adjustments during the Maintenance Phase. • In Section 4.4.1 description of steps for subjects that previously underwent radiation was clarified to include appropriate timing for entry into Extended Evaluation Phase if appropriate. • In Section 4.5 (previously Section 4.3) visit timing for Extended Evaluation Visits, including visit windows, was added (every 90 days ± 14 days). Information about the Follow-Up Visit, with its timing of at least 14 days and within 30 days of completion of treatment was added. • Combined elements of prior Inclusion Criteria #3 and #4, which were errantly mutually exclusive, to reflect the spectrum of disease diagnoses required for inclusion. Inclusion criteria renumbered. • Updated Inclusion Criteria #6 (previously #7) to clarify that evidence of improvement should

	not be exhibited within the 6 months prior to the screening visit. • Clarified Inclusion Criteria #7 (previously #8) to indicate that a minimum of 6 weeks rather than 3 months should elapse before the subject can be deemed a surgical failure and subjects should have no significant post-operative sequelae. • Changed washout interval for pasireotide LAR to 12 weeks from 8 weeks (Inclusion Criteria #8). • Clarification of Inclusion Criteria #9 (previously #10) to indicate that megestrol acetate and medroxyprogesterone acetate are different medications, which are both excluded for use during the study. • Section 5.3.2 hepatitis testing has been updated to clarify that the section addresses both Withdrawals and/or Re-Challenge. The testing for causality has been clarified to include testing for Hepatitis [A, B, C, E], autoimmunity and imaging and clarified additional follow-up for liver-related AESIs. • Section 6 has been updated to include references to Appendix D, Appendix E and Appendix F for governance of study execution and reporting. • The evaluation of signs and symptoms of CS is not required as part of the additional safety evaluations required for each dose escalation beyond 600 mg/day. The text in Section 6.2.1, which included this assessment, was not aligned with Section 4.2.1 and has been deleted. • Section 6.2.4.1 has been updated to include the collection of an additional PK sample as close to the time of the event as possible. The definition of persistent and confirmed QTc prolongation was added with corresponding references to related sections and Appendices. The additional sample collection was also included in Section 6.2.8.1. • Section 6.2.4.2 has been updated to include timing of ECG evaluation following resumption of dosing as being within 1-2 hours of dosing.

	• In Section 6.2.5 the testing for FSH was clarified to be for women only. • Table 2 (previously Table 3) has been updated to clarify that the values are minimum values for subjects ranging from 18 to 70 years and that adequate creatinine excretion rates for subjects over 70 years of age should be discussed on a case by case basis with the Medical Monitor. • Section 6.2.6.1 and Appendix A have been revised to remove the extra 24-hour urine collection at start of Maintenance Phase (M1 visit), as this is collected at end of titration phase. • Section 6.2.7 and subsections were added to clarify situations where additional safety monitoring is required. • In Section 6.2.7.3 and Section 6.3.2, updated information about Adrenal Insufficiency and acute adrenal crisis. • Section 6.2.8.1 has been updated to clarify the timing of PK sampling. • Clarified section numbering and heading levels in Section 6.3. • Section 7 was clarified to indicate that the substances were to be avoided throughout the study, including a change from blood oranges to Seville oranges (i.e., sour orange bigarade orange, or marmalade orange). Clarifications were also made to indicate that licorice should be avoided throughout the study. • In Section 7, the restrictions associated with cortisol testing (urine and salivary) were aligned with the subject instructions and now include brushing teeth up to 2 hours prior to salivary testing, and any type of chewing, eating or drinking up to 1 hour prior to salivary testing. • Section 8.4 has been revised to reflect that a data restriction plan (DRP) will be used to govern the availability of efficacy data, rather than an SOP as originally stated. • Section 10.2 has been updated to advise that when no alternative medications are available, Investigators may seek permission from the Medical Monitor concerning subjects taking

	medications that cause QTc prolongation. This has also been clarified in Appendix J. • Section 10.3 has been updated to clarify those medications that should be used with caution. • Added wording in Section 11.1 and Appendix A clarifying the timing of the Follow-Up Visit approximately 2 weeks following termination of treatment with COR-003 (early withdrawal or M12 at the end of the Extended Evaluation Phase). Updated Appendix references, including clarifying all Appendix references to ensure alignment with appropriate Appendix. • Sections 12.5.1.3, (clinical laboratory data) 12.5.1.4 (vital signs) and 12.5.1.5 (ECG) have been revised to remove hypothesis tests. These data will be summarized but not tested. Additionally, QTc values of clinical importance have been added as Table 6 in Section 12.5.1.5. • Section 12.5.2.1 has been revised to clarify that the treatment estimate of the clinical response rate at the end of the Maintenance Phase and its associated two-sided 95% confidence interval (CI) will be obtained from a repeated measures generalized estimating equation (GEE) model with a logit link using SAS PROC GENMOD GLIMMMIX with LSMEANS statement. Also that the longitudinal model will include visit, the concurrent CS medical conditions (diabetes, hypertension) as Baseline covariates as well as age (rounded median split), sex, disease duration, prior CS therapy, and prior radiation therapy, and subject will be included as a random effect. The previous text regarding time trends has been deleted. • In Section 12.5.2.2 the analysis of Salivary and Serum Cortisol has been revised to clarify that change from Baseline, percent change from Baseline and at-visit values will be listed and summarized descriptively by visit, and a paired t-test will be used to compare post-baseline values with baseline values, for each visit. • In Section 12.5.2.2 for the analysis of CS Comorbidity Biomarkers, it has been clarified that the longitudinal model will include visit, the concurrent CS medical conditions (diabetes,

	hypertension) as Baseline covariates as well as age (rounded median split), sex, disease duration, prior CS therapy, and prior radiation therapy, and subject as a random effect. The analysis of time trends and McNemar's tests have been deleted. • In Section 12.5.2.2 for the analysis of the Glucose Tolerance Test and Spot Albumin, a paired t-test has been added for each assessment. • Section 12.5.2.3 it is no longer planned to perform the exact binomial test and 95% CI for and medication changes so these have been removed. Additionally, the text regarding additional exploratory analyses has been deleted as it is redundant. • Addition of cross-referencing throughout. • Reference was added (Schindler) for classification and pharmacology of progestins. • Added DL0 to Appendix A. • Appendix A, footnote 6 has been clarified to indicate that Spaulding ECGs are to be performed at each visit during Maintenance and Extended Evaluation phases monthly. • MRI at the Follow-Up Visit for subjects completing M12 was removed from the Time and Events Table in Appendix A to avoid magnetic resonance images (MRI) being taken within 2 weeks of each other. • Reformatted and expanded Appendix J to clarify Prohibited and Precautionary medications. • Overall minor modifications to wording have been included to increase clarity of protocol.

SPONOSOR APPROVAL

An Open Label Study to Assess the Safety and Efficacy of COR-003 (2S, 4R-Ketoconazole) in the Treatment of Endogenous Cushing's Syndrome

Fredric Cohen, MD
Senior Vice President, Global Research and Development

Signature: _____ Date: 25 October 2016

INVESTIGATOR AGREEMENT

I have read this protocol and agree:

- To conduct the study as outlined herein, in accordance with Good Clinical Practices (cGCPs), 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 IRB or 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: 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] methoxyl]phenyl] piperazine}

Title of Study: An Open Label Study to Assess the Safety and Efficacy of COR-003 (2S, 4R-Ketoconazole) in the Treatment of Endogenous Cushing's Syndrome

Study center(s): A multicenter study in the US and Europe.

Phase of development: Phase 3

Objectives:

Primary:

- To evaluate the clinical responder rate, defined as the proportion of subjects with normal urinary free cortisol (UFC) after 6 months of treatment with COR-003 in the Maintenance Phase without dose increase; and to evaluate the range of effective doses in subjects with various levels of hypercortisolism.

Secondary:

- To identify the proportion of subjects with clinical response, defined as reduction in mean 24-hour UFC levels to below or equal to the upper limit of normal (≤ ULN) after each month of treatment with COR-003 without a dose increase during the Maintenance Phase;
- To identify the proportion of subjects with complete or partial response, defined as ≥50% reduction of 24-hour UFC levels from Baseline after each of the 6 months of treatment with COR-003 without a dose increase in the Maintenance Phase;
- To characterize changes in 24-hour UFC levels from Baseline during the 6 months of treatment with COR-003 in the Maintenance Phase regardless of dose increases;
- To characterize shifts in normality for 24-hour UFC levels from Baseline during the 6 months of treatment with COR-003 in the Maintenance Phase regardless of dose increases;
- To characterize changes in serum and late night salivary cortisol concentrations during the 6 months of treatment with COR-003 in the Maintenance Phase;
- To assess the effects on Clinical Signs and Symptoms of CS, the quality of life (QoL) measures obtained from the Cushing QoL questionnaire and the severity of depression obtained from the Beck's Depression Inventory II in the Maintenance Phase;
- To evaluate changes in the biomarkers of CS comorbidities (diabetes, hypertension, hypercholesterolemia and obesity) in the Maintenance Phase;
- To assess the safety and tolerability of COR-003.

Exploratory:

- To assess the clinical responder rate (defined for the initial inference of efficacy as the proportion of subjects with normal 24-hour UFC levels after 6 months of

treatment with COR-003 in the Maintenance Phase without dose increase) beyond 6 months of treatment (Extended Evaluation Phase);

- To assess the proportion of subjects with complete or partial response (defined for the initial inference of efficacy as ≥50% reduction of 24-hour UFC levels from Baseline after 6 months of treatment with COR-003 in the Maintenance Phase without dose increase) beyond 6 months of treatment (Extended Evaluation Phase);
- To characterize changes in 24- hour UFC levels from Baseline beyond 6 months of treatment with COR-003 (Extended Evaluation Phase);
- To characterize shifts in normality for 24-hour UFC levels from Baseline beyond 6 months of treatment with COR-003 (Extended Evaluation Phase);
- To characterize changes in serum and late night salivary cortisol concentrations beyond 6 months of treatment with COR-003 (Extended Evaluation Phase);
- To assess the effects on Clinical Signs and Symptoms of CS, the QoL measures obtained from the Cushing QoL questionnaire and the severity of depression obtained from the Beck's Depression Inventory II beyond 6 months of treatment with COR-003 (Extended Evaluation Phase);
- To evaluate changes in the biomarkers of CS comorbidities (diabetes, hypertension, hypercholesterolemia and obesity) beyond 6 months of treatment with COR-003 (Extended Evaluation Phase);
- To describe the Clinical Benefit after 6 months of treatment with COR-003 in the Maintenance Phase, and after 9 and 12 months of treatment (Extended Evaluation Phase), defined as follows:
    - Clinical response as indicated by UFC ≤ upper limit of normal (ULN), and
    - No increase in COR-003 dose during Maintenance Phase, and
    - A clinically meaningful improvement in any one Baseline CS comorbidity (diabetes, hypertension, hypercholesterolemia, weight) as defined in the Statistical Analysis Plan (SAP), and
    - No study drug related treatment-emergent adverse event (TEAE) classified as severe or worse.
- To assess changes in anti-diabetic, anti-cholesterol and antihypertensive therapies after 6 months of treatment with COR-003 in the Maintenance Phase, and after 9 and 12 months of treatment (Extended Evaluation Phase);
- To assess the change in clinical signs of hypercortisolism obtained from standardized photographs and rated by an adjudication committee after 3 and 6 months of treatment with COR-003 in the Maintenance Phase, and after 12 months of treatment (Extended Evaluation Phase).

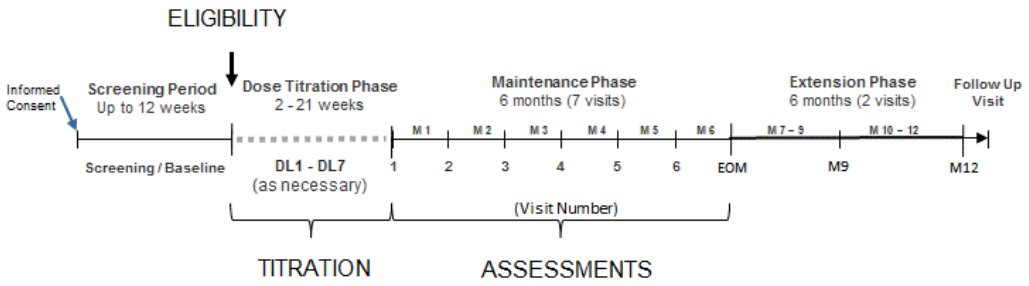
Pharmacokinetic/Pharmacodynamic:

- To evaluate the pharmacokinetics (PK) of COR-003 in subjects with CS;
- To explore the dose-response relationship for safety, including dose-response for adverse events of special interest (AESI) such as QTc if data allow;
- To explore the dose-response relationship for reduction of UFC levels if data allow.

Methodology: This is a single arm, open label, dose titration study to assess efficacy, safety, tolerability, and PK of COR-003 in subjects with endogenous CS as illustrated below. The

range of effective doses for COR-003 in this CS population will also be established. Following an initial screening and washout period, as applicable, this study will be conducted in three treatment phases as follows:

- **Dose Titration Phase**: approximately 2 to 21 weeks to achieve an effective and tolerable maximum dose (the Therapeutic Dose);
- **Maintenance Phase**: 6 months of treatment at the Therapeutic Dose following the Dose Titration Phase;
- **Extended Evaluation Phase**: 6 months of continued treatment after the Maintenance Phase.



After signing the informed consent, subjects will enter the Screening Phase. After the initial assessments, subjects on previous CS medical therapies or other prohibited medications must enter a washout period before completing all Screening assessments detailed in the Time and Events Table. Baseline measurements will be obtained as part of the Screening assessments after washout and completion of all initial Screening procedures. If a subject does not meet the eligibility requirements, they might be eligible to re-screen but only if their underlying condition has changed in the interim such that they are now likely to meet 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.

After confirmation of eligibility at the Baseline Visit including confirmation of increased UFC levels as per eligibility requirements, subjects will enter into the Dose Titration Phase. Dose titration will occur in increments of 150 mg with a starting dose of 150 mg twice daily (BID) over a period of approximately 2 to 21 weeks to achieve an effective and tolerable maximum dose (the Therapeutic Dose). Decisions for dose increases will be based on each subject's tolerability, assessment of UFC levels and safety data. Dose decreases may also occur based on subject's tolerability and safety data.

Subjects that reach total daily doses of >600 mg/day will be monitored more closely and will be asked to return 7 days (±3 days) following each dose escalation visit at total daily doses >600 mg/day for an additional safety evaluation. Subjects will be advised to contact the Investigator immediately in the event of developing symptom-specific adverse events (AE), such as adrenal insufficiency or other AEs at any time.

Once the Therapeutic Dose has been reached and confirmed from the mean of a total of four adequately collected 24-hour urine collections for UFC measurements, subjects will enter into the Maintenance Phase of the study and will be asked to return to the clinic monthly [every 30 days (±7 days)] for 6 months for assessment of efficacy and safety. During the Maintenance Phase, doses may not be increased to maintain UFC levels at or below ULN of the assay unless it is confirmed that a dose increase is deemed medically necessary at the

discretion of the Investigator after discussion with the Medical Monitor. Prior to the End of Maintenance Phase Visit, four complete 24-hour urine collections will be obtained and subjects may enter the Extended Evaluation Phase.

In the 6-month Extended Evaluation Phase, subjects will return to the clinical site every 90 days (±14 days) for safety and efficacy evaluations.

In order to exclude that a treatment effect is due to delayed onset of radiation therapy, previously irradiated subjects must stop treatment with COR-003 for at least 2 weeks after the end of the 6-month Maintenance Phase (End of Maintenance Phase Visit) and provide four complete 24-hour urine collections for UFC measurements at least 14 days following the End of Maintenance Phase Visit. If the 24-hour UFC results indicate that UFC levels are elevated, the subject may subsequently restart therapy and continue into the Extended Evaluation Phase, at the discretion of the Investigator. They should return for their next in-clinic visit for study assessments and resupply of study medication every 3 months [every 90 days (± 14 days)] from the End of Maintenance Visit.

Throughout the study, safety data will be collected at specified times. Adequate medical coverage will be provided at all times during the course of the study to ensure that prompt safety decisions can be made and appropriate medical interventions are provided. The Investigator will provide subjects with instructions on how to access the medical staff regardless of day and time in order to obtain medical care. An independent Data Safety Monitoring Board (DSMB) will review the safety of the drug throughout the study

After completion of treatment in this study, subjects who do not extend treatment through the expanded access program, will have a Follow-Up Visit (a minimum of 2 weeks and no longer than 30 days following the completion of treatment). Once all study assessments have been completed, subjects will be promptly referred back to their endocrinologist (if not the Investigator) for further management according to the local standard of care, and based on their preceding medical history. [NOTE: The Follow-Up Visit is not required for subjects continuing into expanded access treatment.]

Number of subjects (planned): A sufficient number of subjects (estimated at approximately 90) will be enrolled into the Dose Titration Phase of the study to ensure that at least 70 subjects complete the 6-month Maintenance Phase.

Inclusion Criteria:

Subjects will be eligible for the study if all of the following criteria are met:

1. Male or female ≥18 years of age
2. Able to provide written informed consent prior to any study procedures being performed; eligible subjects must be able to understand the informed consent form prior to inclusion into the study.
3. Confirmed diagnosis of newly diagnosed, persistent or recurrent Cushing's disease (CD) or endogenous CS of other etiology if subjects are not candidates for surgery or radiotherapy within the 18 months after enrollment.

   Previous medical records will be collected and used to support the diagnosis of CD or endogenous CS of other etiology, including the following etiologies:

   - Ectopic adrenocorticotropic hormone (ACTH) secretion, i.e. ACTH not of pituitary origin
   - Ectopic corticotropin-releasing hormone (CRH) secretion
   - Adrenal-dependent CS (i.e. adrenal adenoma (NOT carcinoma), adrenal hyperplasia, etc.)
   - Etiology unknown.

In the absence of pathological or post-surgical confirmation of the diagnosis of CD (i.e. documented adrenal insufficiency post-adenomectomy or hypophysectomy, which will be considered diagnostic). The following historical evidence will be considered satisfactory to establish the diagnosis of CD:

Plasma corticotropin (ACTH) level >20 pg/mL (4.5 pmol/L) or greater (Note: ACTH ≥5 pg/mL (1.1 pmol/L) and ≤20 pg/mL will generally suffice only if accompanied by either a positive CRH stimulation test or Dexamethasone Suppression Test (DST) or combined CRH-DST) PLUS one of the diagnostic strategies described below based on pituitary magnetic resonance imaging (MRI)/computed tomography (CT) findings (Note: pituitary imaging preceding the original diagnosis is a requirement for eligibility):

For tumors ≥6 mm by imaging:

- Inferior petrosal sinus sampled (IPSS) ACTH central:plasma gradient ≥2 before CRH or ≥3 after CRH, OR if IPSS was not done then:
- Positive ACTH and/or cortisol response to CRH/desmopressin or combined CRH-desmopressin stimulation plus high-dose (8 mg) dexamethasone suppression of plasma cortisol, ideally on more than one occasion, performed and interpreted according to internationally recognized standards of diagnosis
- In the absence of IPSS and the combination of tests described, 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.

For tumors <6 mm or not visible by MRI:

- IPSS with ACTH central:plasma gradient ≥2 before CRH or ≥3 after CRH
- 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. Regardless of the etiology of endogenous CS, subjects MUST have elevated mean 24-hour UFC levels ≥1.5X ULN based on the normative range of the central lab assay and on a minimum of four measurements from adequately collected urine. Urine will ideally be collected on sequential days.
5. In addition to elevated mean UFC, presence of abnormal values from **one** of the following tests:
    - Abnormal DST: Elevated 8 AM serum cortisol ≥1.8 µg/dL (50 nmol/L) after 1 mg dexamethasone orally at 11 PM the evening prior (if not conducted already in the diagnostic workup of the subject within the previous 2 months before start of Screening Phase; in that case previous test results and details of conduct will need to be available by the Baseline Visit)
    - Elevated late night salivary cortisol concentrations (at least two measurements) >ULN

    NOTE: For subjects with estimated glomerular filtration rate (eGFR as determined by Modified Diet in Renal Disease MDRD equation) >40 and <60 mL/min/1.73 m^2 in addition to meeting the UFC criteria, late night salivary cortisol test results (≥2 measurements) **MUST** also demonstrate evidence of CS.
6. Previously irradiated subjects with CD or endogenous CS of other etiology will be allowed as long as the radiation treatment occurred > 4 years ago and subjects have not exhibited evidence for improvement in their underlying CD for 6 months prior to the

Screening visit. The total number of previously irradiated subjects enrolled in this study will not exceed 10.

7. Subjects with CD or CS of other etiology who are not candidates for surgery, refuse surgery, or in whom surgery will be delayed for at least 18 months following enrollment. Subjects may be allowed to participate in the trial while awaiting surgery, but must agree to complete this study prior to surgery. For subjects who have already undergone surgery, a minimum of 6 weeks should have elapsed before the subject can be deemed a surgical failure. Subjects who have undergone surgery should be stable post-surgery (i.e., no significant post-operative sequelae remain and the risk of such sequelae is considered negligible).
8. Subjects on treatment for CD or endogenous CS of other etiology for whom treatment has been inadequate or not well tolerated must agree to the following minimum washout periods prior to the Baseline Visit:
    - 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
9. Subjects on megestrol acetate or medroxyprogesterone acetate (and selected other synthetic progestins) must agree to a washout period of at least 6 weeks prior to the Baseline Visit
10. A female is eligible to enter and participate in the study if she is of:
    Non-child bearing potential (i.e. physiologically incapable of becoming pregnant, including any female who is post-menopausal or surgically sterile). Surgically sterile females are defined as those with a documented hysterectomy and/or bilateral oophorectomy or tubal ligation.
    Post-menopausal females are defined as being amenorrheic for greater than 1 year with an appropriate clinical profile, e.g. age > 45 years, in the absence of hormone replacement therapy. However, in questionable cases, a blood sample with follicle stimulating hormone (FSH) > 40MIU/ml and estradiol < 40pg/ml (<140 pmol/L) is confirmatory.

    OR

    Child-bearing potential and agrees to use highly effective methods of birth control while participating in the study and for 2 weeks after the study is completed.
11. Fertile men must also agree to use a medically acceptable form of birth control while on study drug and up to 2 weeks after the study is completed.
12. Able to comprehend and comply with procedures.

Exclusion Criteria

Subjects will be excluded from the study if any of the following criteria are met:

1. Subjects with Pseudo-Cushing's syndrome based on assessment of the Investigator.
2. Subjects with cyclic CS based on assessment of the Investigator
3. Subjects with a non-endogenous source of hypercortisolism such as exogenous source of glucocorticoids or therapeutic use of ACTH.
4. Known inherited syndrome as the cause of hypercortisolism, including but not limited to multiple endocrine neoplasia Type 1, McCune Albright Syndrome and Carney Complex

5. Subjects with adrenal carcinoma
6. History of malignancy, other than thyroid, early stage prostate, squamous cell and basal cell carcinoma, within 3 years prior to the Screening Phase. Subjects with history of such allowed carcinoma must have a life expectancy of >18 months and must be considered medically stable. Subjects with early stage prostate cancer undergoing no treatment due to low grade potential may be enrolled.
7. Clinical or radiological signs of compression of the optic chiasm.
8. Major surgery within 1 month prior to enrollment (informed consent form signing)
9. Subjects with clinically significant abnormality in 12-lead ECGs during the Screening Phase needing medical intervention.
10. Subjects with QTc interval of >470 msec during the Screening Phase.
11. Subjects with a history of Torsades des Pointes, or ventricular tachycardia, or ventricular fibrillation, or history of prolonged QT syndrome (including family history), or use of medications resulting in QT/QTc prolongation, or hypokalemia <3.0 meq/L.
12. Pre-existing hepatic disease; subjects with mild to moderate hepatic steatosis consistent with fatty infiltration (non-alcoholic fatty liver disease [NAFLD] are allowed).
13. Positive for hepatitis B surface antigen (HbsAg) or positive hepatitis C test.
14. History or symptoms of recurrent symptomatic cholelithiasis or pancreatitis.
15. Liver function tests (LFT) must not be above the following cut-offs during the Screening Phase:
    - Alanine transaminase (ALT) and/or aspartate transaminase (AST) >3 X ULN
    - Total bilirubin (TBN) >2 X ULN

    If all LFTs are within normal limits (WNL) and TBN is elevated, examination of direct and indirect bilirubin may be conducted. Subjects with isolated indirect TBN up to 3X ULN are presumed to have Gilbert's syndrome and may be enrolled if all other LFTs are within normal levels.
16. History of documented or suspected drug-induced liver injury requiring drug discontinuation of ketoconazole or any azole antifungals.
17. Pregnant or lactating women
18. Human immunodeficiency virus (HIV)-positive.
19. History of persistent uncontrolled hypertension (>180/120 mmHg) despite medical intervention.
20. Subjects with hypercholesterolemia who are currently treated with atorvastatin, lovastatin or simvastatin and not willing or unable to change to alternative therapies, i.e. pravastatin, fluvastatin, or rosuvastatin within 2 weeks of start of the Screening Phase.
21. Body habitus preventing repeated venipuncture as required by protocol.
22. Subject is currently in another study or has received any investigational treatment (drug, biological agent or device) within 30 days or five half-lives of treatment, whichever is longer.
23. Repeated hospitalization for hyperglycemia or for any complication of hyperglycemia and diabetes during the last 12 months
24. Subjects with decreased renal function as defined by eGFR <40 mL/min/1.73 m^2, using MDRD equation.
25. 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 to perform the necessary procedures (for example, psychiatric instability or severe disability).

26. Abnormal free thyroxine (T4). Subjects with thyroid stimulating hormone (TSH) < lower limit of normal (LLN) and normal free T4 are permitted to participate in the study.
27. Subjects who have a history of alcohol or drug abuse in the 6-month period prior to enrollment.
28. Subjects who have been treated with mitotane within 6 months of the Screening Phase.
29. Subjects who are currently taking any H2 receptor antagonists, proton-pump inhibitors, or sucralfate (all of which inhibit absorption of COR-003). A list of orally acceptable antacids (for example, Mylanta and Maalox) will be provided, and can only be taken a minimum of 2 hours **after** dosing of COR-003.
30. Subjects who receive any prohibited concomitant medication and cannot discontinue it safely prior to the Baseline Visit, including but not limited to the following:
    - Weight loss medications (prescription or over the counter);
    - Acetaminophen (paracetamol) >3 g total daily dose;
    - Strong **inducers or inhibitors** of CYP3A4 enzyme system that may interfere with the metabolism of COR-003 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 might pose unacceptable risks due to overlapping toxicities (e.g. QT prolongation, liver toxicity);
    - Genuine licorice.

Investigational product, dosage and mode of administration:

COR-003 (2S,4R ketoconazole); 150 mg immediate release tablets for oral BID dosing; total daily dose will be titrated in 150 mg increments from a starting dose of 300 mg up to a maximal daily dose of 1200 mg (Doses can be reduced and can be as low as 150 mg daily.)

Duration of treatment:

Subjects will undergo dose titration over approximately 2 to 21 weeks until achieving efficacy at their individual therapeutic dose, followed by 6 months of dosing at that dose level (Maintenance Phase). All subjects completing the Maintenance Phase will be eligible to be rolled over into an Extended Evaluation Phase for another 6 months of follow-up, for a total treatment duration of approximately 1 year (exclusive of the dose titration period).

Reference therapy, dosage and mode of administration:

None; this will be a single arm, uncontrolled study of oral administration of COR-003 (2S,4R-ketoconazole).

Analysis Populations:

Intent-to-Treat (ITT) Population: The ITT population will include all subjects who receive at least one dose of COR-003. This population will be used for the evaluation of efficacy and all safety analyses.

Maintenance (M) Population: The M population will consist of all subjects who enter the Maintenance Phase of the study. This population will be used for the supportive evaluation of all the primary and secondary efficacy endpoints.

Per Protocol (PP) Population: The PP population will consist of all subjects who enter the Maintenance Phase of the study and have no major protocol deviations that may affect efficacy. This population will be as supportive analysis for the analysis of the primary endpoint.

Criteria for evaluation:

Primary endpoint:

- Proportion of subjects with response to COR-003, defined as reduction in mean 24-hour UFC levels to ≤ ULN following 6 months of Maintenance Phase therapy without a dose increase during that phase, summarized by Maintenance Phase dose level and overall.

Secondary endpoints:

- Proportion of subjects with clinical response to COR-003, defined as mean UFC level ≤ ULN, to be determined after 1, 2, 3, 4, and 5 months of dosing without a dose increase in the Maintenance Phase;
- Proportion of subjects with complete or partial response to COR-003, defined as mean UFC level ≥ 50% reduction from Baseline after 1, 2, 3, 4, 5 and 6 months of dosing without a dose increase in the Maintenance Phase;
- Change and percentage change from Baseline in mean 24-hour UFC levels after 1, 2, 3, 4, 5 and 6 months of dosing in the Maintenance Phase regardless of dose increases;
- Shift in UFC normality categories from Baseline to 1, 2, 3, 4, 5 and 6 months of dosing in the Maintenance Phase regardless of dose increases;
- Change and percentage change from Baseline in serum and late night salivary cortisol levels after 1, 2, 3, 4, 5 and 6 months of dosing in the Maintenance Phase;
- Changes from Baseline in Clinical Signs and Symptoms of CS after 1, 2, 3, 4, 5 and 6 months of dosing in the Maintenance Phase;
- Changes from Baseline in the QoL measures obtained from the Cushing QoL questionnaire and the severity of depression obtained from the Beck's Depression Inventory II after 3 and 6 months of dosing in the Maintenance Phase;
- Change from Baseline in CS comorbidities biomarkers (fasting glucose, hemoglobin A1C [HbA1c], systolic blood pressure [SBP], diastolic blood pressure [DBP], total cholesterol, low and high density lipoproteins [LDL, HDL, respectively], and body weight) after 1, 2, 3, 4, 5 and 6 months of dosing in the Maintenance Phase;
- Changes from Baseline for oral glucose tolerance test (OGTT) (pre-diabetics only) and spot albumin/creatinine ratio as a measure of microalbuminuria (only if abnormal at Baseline) after 3 and 6 months of dosing in the Maintenance Phase;
- Changes from Baseline for C-reactive protein (CRP) after 1, 2, 3, 4, 5 and 6 months of dosing in the Maintenance Phase;
- Safety evaluations will include clinical observations and AE reporting, vital signs (SBP, DBP, body weight, body mass index [BMI]), electrocardiograms (ECGs), hematology, chemistry panels (inclusive of expanded markers of liver function, ACTH, Insulin-like Growth Factor-1 [IGF-1] and testosterone concentrations), dipstick urinalysis (microscopic evaluation, if dipstick positive), tumor size by MRI as applicable.

Exploratory endpoints:

- Proportion of subjects with long-term clinical response to COR-003, defined as mean UFC level ≤ ULN, after 9 and 12 months (Extended Evaluation Phase);
- Proportion of subjects with long-term complete or partial response to COR-003, defined as mean UFC level ≥ 50% reduction from Baseline after 9 and 12 months (Extended Evaluation Phase);
- Change and percentage change from Baseline in mean 24-hour UFC levels after 9 and 12 months (Extended Evaluation Phase);
- Shift in UFC normality categories from Baseline at 9 and 12 months (Extended Evaluation Phase);
- Change and percentage change from Baseline in serum and late night salivary cortisol levels after 9 and 12 months (Extended Evaluation Phase);
- Changes from Baseline in Clinical Signs and Symptoms of CS, on the QoL measures obtained from the Cushing QoL questionnaire, and on the severity of depression obtained from the Beck's Depression Inventory II after 9 and 12 months of dosing (Extended Evaluation Phase);
- Change from Baseline in CS comorbidities biomarkers (HbA1c, SBP, DBP, total cholesterol, LDL, HDL and body weight) after 9 and 12 months of dosing (Extended Evaluation Phase);
- Changes from Baseline for OGTT (pre-diabetics only) and spot albumin/creatinine ratio as a measure of microalbuminuria (only if abnormal at Baseline) after 9 and 12 months of dosing (Extended Evaluation Phase);
- Changes from Baseline for CRP after 9 and 12 months of dosing (Extended Evaluation Phase);
- Clinical benefit rate determined after 1, 2, 3, 4, 5 and 6 months of dosing in the Maintenance Phase and at 9 and 12 months (Extended Evaluation Phase). Clinical benefit is defined as follows:
    - Clinical response as indicated by UFC ≤ ULN, and
    - No increase in COR-003 dose during Maintenance Phase, and
    - A clinically meaningful improvement in any one Baseline CS comorbidity (diabetes, hypertension, hypercholesterolemia, weight) as defined in the SAP and
    - No study drug related TEAE classified as severe or worse;
- Changes in the doses of concomitant medications and in particular anti-diabetic, anti-cholesterol and antihypertensive medications after 6 months of dosing with COR-003 during the Maintenance Phase and during the Extended Evaluation Phase relative to Baseline doses of such medications;
- Changes in the severity score for clinical signs of hypercortisolism obtained from standardized photographs and rated by an adjudication committee after 3 and 6 months of dosing with COR-003 during the Maintenance Phase at 12 months in the Extended Evaluation Phase.

Pharmacokinetic Endpoints and Pharmacokinetic/Pharmacodynamic Modeling:

- Estimate the following parameters using population PK modeling: 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.

- Estimate the following pharmacodynamic parameters: COR-003 concentration producing half-maximal UFC suppression (IC50), the maximal suppression of UFC (Imax) and associated estimates of between subject variability, if feasible. The range of UFC reduction by dose will be explored.
- Other safety and efficacy endpoints will also be explored graphically by dose or summary metrics of exposure.
- The relationship of AESI including QTc interval to dose of COR-003 will be evaluated if data allow.
- The relationship of UFC reduction to dose of COR-003 will be evaluated if data allow.

Statistical methods:

Primary Efficacy Endpoint: The treatment estimate of the clinical response rate at the end of the Maintenance Phase and its associated two-sided 95% confidence interval (CI) will be obtained from a repeated measures GEE model with logit link using SAS PROC GLIMMIX with LSMEANS statement. The primary analysis will be the ITT population and analysis will be repeated in the Maintenance population and Per Protocol population.

Secondary Efficacy Endpoints: Analyses of response rates will be analyzed as described for the primary endpoint.

Calculations for the biomarkers of CS comorbidity (fasting glucose, HbA1c, SBP, DBP, total cholesterol, LDL, HDL, and body weight) will be performed using SAS PROC MIXED to account for all post-Dose Titration Phase outcomes per subject with changes from Baseline and two-sided 99% lower confidence bounds calculated using LSMEANS.

Changes from Baseline in serum and late night salivary cortisol, and scores from the Cushing's QoL and Beck's Depression questionnaires, will be summarized by time point using descriptive statistics and analyzed using paired t-test.

Safety Analyses: Safety assessments, including AEs, vital signs, ECGs (inclusive of QTc), laboratory parameters, and physical examinations will be summarized using descriptive statistics by time point.

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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
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
BIPSS	Bilateral inferior petrosal sinus sampling
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
CRP	C-reactive protein
CS	Cushing´s syndrome
CT	Computed tomography
CYP	Cytochrome P450
GCP	Good Clinical Practice
DBP	Diastolic blood pressure
DCCT	Diabetes Control and Complications Trial
DILI	Drug-induced liver injury
DL	Dose level
DRP	Data restriction plan
DSMB	Data Safety Monitoring Board
DST	Dexamethasone Suppression Test
EAP	Expanded Access Program
E/T	Early termination
ECG	Electrocardiogram/electrocardiograph
eGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GEE	Generalizing estimating equation
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
GR	Glucocorticoid receptor
GTT	Glucose tolerance test
HbsAg	Hepatitis B surface antigen
HbA1c	Hemoglobin A1C

HDL	High density lipoprotein
HDPE	High Densitiy polyethylene
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	Human immunodeficiency virus
HPLC/MS/MS	High pressure liquid chromatography tandem mass spectroscopy
HR	Heart rate
IC50	Half-maximal suppression
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IGF-1	Insulin-like Growth Factor-1
Imax	Maximal suppression of UFC
IPSS	Inferior petrosal sinus sampling
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent-to-treat
IU	International Unit
IUD	Intrauterine device
Ka	Absorption rate constant
LDL	Low density lipoprotein
LFT	Liver function test
LLN	Lower limit of normal
LOCF	Last observation carried forward
LSMEAN	Least Squares Mean
M	Maintenance
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
mITT	Modified intent-to-treat
MR	Mineralocorticoid receptor
MRI	Magnetic Resonance Imaging
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NCI-CTCAEv4	National Cancer Institute Common Terminology for Adverse Events, Version 4.0
NGSP	National Glycohemoglobin Standardization Program
OGTT	Oral glucose tolerance test
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per protocol
PR	Progesterone receptor
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
RLOCF	Restricted last observation carried forward
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SOP	Standard operating proceure
SPM	Study procedures manual
t½	Half-life
T4	Thyroxine
T2DM	Type 2 diabetes mellitus
TBN	Total bilirubin
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitors
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
WNL	Within normal limits

1 INTRODUCTION

1.1 Disease Background

Endogenous Cushing´s syndrome (CS) is a rare, serious and potentially lethal endocrine disease caused by chronic elevated cortisol exposure to human organs. The incidence of CS has been estimated to be 2-3 cases per million per year [Lindholm 2001, Steffensen 2010]. The prevalence of CS has been reported to be 30-60 cases per million [Dalton 1974, Kreutzer 2009, Pivonello 2005, Sharma 2011]. Patients with incompletely controlled disease are seriously ill and have a 4 to 5-fold higher mortality rate than age- and gender matched controls, mainly due to metabolic and cardiovascular complications [Lindholm 2001, Mancini 2004, Pivonello 2005].

Treatment options for CS include surgery, radiation therapy and medical treatment. Medical treatment is used to suppress excessive cortisol production or activity and ameliorate its clinical manifestations, prior to surgery, in patients awaiting the effects of radiation therapy [Nieman 2002], or in cases when surgery is delayed, contraindicated, or unsuccessful. As such, normalization of 24-hour urinary free cortisol (UFC) and normal serum or plasma cortisol levels from a low-dose overnight dexamethasone suppression test (DST) are considered adequate markers of disease remission [Bochicchio 1995]. More recently, measurement of late night salivary cortisol levels is gaining clinical importance. Conversely, the persistence of high or only modestly reduced UFC levels argues for treatment failure.

Ketoconazole (Nizoral®, comprised of two enantiomers: 2S,4R- and 2R,4S-ketoconazole) is an antifungal agent that, at higher dosages, reduces adrenal steroid production via inhibition of multiple steroidogenic enzymes, e.g. 11β-hydroxylase, 17α-hydroxylase and aldosterone synthase [Engelhardt 1991, Sonino 1987, Nizoral 2002]. One publication has reported a direct effect on ectopic adrenocorticotropic hormone (ACTH) secretion by ketoconazole. [Steen 1991]. Because of these properties of ketoconazole, it 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].

When patients are treated with ketoconazole, adrenal insufficiency is avoided by adjusting the dose to allow normal cortisol levels. The most frequent adverse effects of ketoconazole are nausea, vomiting, abdominal pain and pruritus. Abnormal liver function tests (LFTs), primarily of the hepatocellular type, can occur. Rarely does severe hepatotoxicity occur. Early markers for these side effects are elevations in serum alkaline phosphatase (AP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin, which are monitored at regular intervals during treatment [Ketoconazole 2014 HRA Assessment Report, Nizoral 2013 Product Insert, Lake-Bakaar 1987; Lewis 1984].

Cortendo AB is developing COR-003, also known as levoketoconazole, the 2S,4R enantiomer of ketoconazole, as an investigational new drug for the treatment of cortisol hypersecretion in CS. It is hypothesized that COR-003 may prove to be both safer and more efficacious than ketoconazole.

COR-003 has a significantly lower IC50 (50% inhibitory concentration) towards key enzymes in cortisol synthesis (11β -hydroxylase, IC50 = 150 nM; 17-α-hydroxylase [CYP17], 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, unpublished results from Moulder Center for Drug Discovery Research, Temple University School of Pharmacy, 2012]. In rats, COR-003 was more potent with respect to reducing corticosterone (the major glucocorticoid in rodents) than either the 2R, 4S-enantiomer or ketoconazole [Cortendo Report Number 2002-02-21].

Although elevations in LFTs associated with ketoconazole [Daneshmend 1988, Kucers 1997, Whitehouse 1994] are generally modest in nature and reversible following cessation of treatment, in rare cases (1 in 10,000 to 15,000 patients) severe hepatotoxicity may occur [Lewis 1984], and in extremely rare cases this adverse reaction may be irreversible and life-threatening. Preclinical data suggest that COR-003 may pose less risk to impair hepatic function than ketoconazole. 2S,4R-ketoconazole has 12-fold higher IC50 towards CYP7A (IC50 = 2.4 μM) 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 such as ketoconazole itself.

Another property that suggests potentially improved safety of 2S,4R-ketoconazole 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 COR-003 [Gerber 2003, Schindler 2003, Schwartz 2008]. The enantiomers in ketoconazole are present in equal amounts, but following ketoconazole oral administration blood 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. Reduced hepatic exposure to the 2S,4R enantiomer (COR-003) may be of value in reducing the liver function abnormalities observed following administration of racemic ketoconazole.

COR-003 has been previously administered to healthy volunteers and human subjects with Type 2 Diabetes Mellitus (T2DM). Doses of COR-003 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 all of these studies, with an adverse effect profile similar to that of ketoconazole. Please refer to the Investigator's Brochure for a detailed description of all prior preclinical and clinical studies conducted with COR-003.

1.2 Rationale for Study Design

This study is the first and pivotal clinical trial investigating the safety and efficacy of COR-003 in subjects with endogenous CS. 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. An open label, single arm design was chosen, since a

concurrent placebo control as monotherapy was deemed unethical, and an approved drug to serve as active control (monotherapy) or as background therapy (adjunctive therapy) suitable for an international study population was unavailable. Pasireotide, which is approved in the EU and US, has a different mode of action at the tumor level and therefore an indication for Cushing's disease (CD) only, and is an injectable with a different safety profile, including hyperglycemia, which would preclude blinding and confound evaluation of efficacy and safety signals.

The chosen design has considered the reported experience treating CS patients with ketoconazole [Castinetti 2014]. Like ketoconazole, dosing of COR-003 needs to be individualized, since therapeutic need varies considerably among patients. Response to therapy (i.e. normalization of UFC and 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 an initial Dose Titration Phase that will identify a tolerable and effective dose for each subject, which will then be administered during the subsequent Maintenance Phase of the study, intended to be without further dose increases. The Maintenance Phase was designed to demonstrate durability of the therapeutic response and, together with the Extended Evaluation Phase, provides long-term efficacy and safety data.

2 OBJECTIVES

2.1 Primary Objective

- To evaluate the clinical responder rate, defined as the proportion of subjects with normal UFC after 6 months of treatment with COR-003 in the Maintenance Phase without dose increase, and to evaluate the range of effective doses in subjects with various levels of hypercortisolism.

2.2 Secondary Objectives

- To identify the proportion of subjects with clinical response, defined as reduction in mean 24-hour UFC levels to below or equal to the upper limit of normal (≤ ULN) after each month of treatment with COR-003 without a dose increase during the Maintenance Phase;
- To identify the proportion of subjects with complete or partial response, defined as ≥50% reduction of 24-hour UFC levels from Baseline after each of the 6 months of treatment with COR-003 without a dose increase during the Maintenance Phase;
- To characterize changes in 24-hour UFC levels from Baseline during the 6 months of treatment with COR-003 in the Maintenance Phase regardless of dose increases;
- To characterize shifts in normality for 24-hour UFC levels from Baseline during the 6 months of treatment with COR-003 in the Maintenance Phase regardless of dose increases;
- To characterize changes in serum and late night salivary cortisol concentrations during the 6 months of treatment with COR-003 in the Maintenance Phase;

- To assess the effects on Clinical Signs and Symptoms of CS, the quality of life (QoL) measures obtained from the Cushing QoL questionnaire and the severity of depression obtained from the Beck's Depression Inventory II in the Maintenance Phase;
- To evaluate changes in the biomarkers of CS comorbidities (diabetes, hypertension, hypercholesterolemia and obesity) in the Maintenance Phase;
- To assess the safety and tolerability of COR-003.

2.3 Exploratory Objectives

- To assess the clinical responder rate (defined for the initial inference of efficacy as the proportion of subjects with normal 24-hour UFC levels after 6 months of treatment with COR-003 in the Maintenance Phase without dose increase) beyond 6 months of treatment (Extended Evaluation Phase);
- To assess the proportion of subjects with complete or partial response (defined for the initial inference of efficacy as ≥50% reduction of 24-hour UFC levels from Baseline after 6 months of treatment with COR-003 in the Maintenance Phase without dose increase) beyond 6 months of treatment (Extended Evaluation Phase);
- To characterize changes in 24-hour UFC levels from Baseline beyond 6 months of treatment with COR-003 (Extended Evaluation Phase);
- To characterize shifts in normality for 24-hour UFC levels from Baseline beyond 6 months of treatment with COR-003 (Extended Evaluation Phase);
- To characterize changes in serum and late night salivary cortisol concentrations beyond 6 months of treatment with COR-003 (Extended Evaluation Phase);
- To assess the effects on Clinical Signs and Symptoms of CS, the QoL measures obtained from the Cushing QoL questionnaire and the severity of depression obtained from the Beck's Depression Inventory II beyond 6 months of treatment with COR-003 (Extended Evaluation Phase);
- To evaluate changes in the biomarkers of CS comorbidities (diabetes, hypertension, hypercholesterolemia and obesity) beyond 6 months of treatment with COR-003 (Extended Evaluation Phase);
- To describe the Clinical Benefit after 6 months of treatment with COR-003 in the Maintenance Phase, and after 9 and 12 months of treatment (Extended Evaluation Phase) as defined in Section 3.3;
- To assess changes in anti-diabetic, anti-cholesterol and antihypertensive therapies after 6 months of treatment with COR-003 in the Maintenance Phase, and after 9 and 12 months of treatment (Extended Evaluation Phase);
- To assess the change in clinical signs of hypercortisolism obtained from standardized photographs and rated by an adjudication committee after 3 and 6 months of treatment with COR-003 in the Maintenance Phase, and after 12 months of treatment (Extended Evaluation Phase).

2.4 Pharmacokinetic/Pharmacodynamic Objectives

- To evaluate the PK of COR-003 in subjects with CS;
- To explore the dose-response relationship for safety, including dose-response for adverse events of special interest (AESI) such as QTc, if data allow;
- To explore the dose-response relationship for reduction of UFC levels, if data allow.

3 ENDPOINTS

3.1 Primary Endpoint

- Proportion of subjects with response to COR-003, defined as reduction in mean 24-hour UFC levels to below or equal to the upper limit of normal (≤ ULN) following 6 months of Maintenance Phase therapy without a dose increase during that phase, summarized by Maintenance Phase dose level and overall.

3.2 Secondary Endpoints

- Proportion of subjects with clinical response to COR-003, defined as mean UFC level ≤ ULN, to be determined after 1, 2, 3, 4 and 5 months of dosing without a dose increase in the Maintenance Phase;

- Proportion of subjects with complete or partial response to COR-003, defined as mean UFC level ≥ 50% reduction from Baseline after 1, 2, 3, 4, 5 and 6 months of dosing without a dose increase in the Maintenance Phase;

- Change and percentage change from Baseline in mean 24-hour UFC levels after 1, 2, 3, 4, 5 and 6 months of dosing in the Maintenance Phase regardless of dose increases;

- Shift in UFC normality categories from Baseline to 1, 2, 3, 4, 5 and 6 months of dosing in the Maintenance Phase regardless of dose increases;

- Change and percentage change from Baseline in serum and late night salivary cortisol levels after 1, 2, 3, 4, 5 and 6 months of dosing in the Maintenance Phase;

- Changes from Baseline in Clinical Signs and Symptoms of CS after 1, 2, 3, 4, 5 and 6 months of dosing in the Maintenance Phase;

- Changes from Baseline in the QoL measures obtained from the Cushing QoL questionnaire and the severity of depression obtained from the Beck's Depression Inventory II after 3 and 6 months of dosing in the Maintenance Phase;
- Change from Baseline in CS comorbidities biomarkers (fasting glucose, hemoglobin A1C [HbA1c], systolic blood pressure [SBP], diastolic blood pressure [DBP], total cholesterol, low and high density lipoproteins [LDL, HDL,

respectively], and body weight) after 1, 2, 3, 4, 5 and 6 months of dosing in the Maintenance Phase;

- Changes from Baseline for oral glucose tolerance test (OGTT) (pre-diabetics only) and spot albumin/creatinine ratio as a measure of microalbuminuria (only if abnormal at Baseline) after 3 and 6 months of dosing in the Maintenance Phase;

- Changes from Baseline for C-reactive protein (CRP) after 1, 2, 3, 4, 5 and 6 months of dosing in the Maintenance Phase;

- Safety evaluations will include clinical observations and adverse event (AE) reporting, vital signs (SBP, DBP, body weight, body mass index [BMI]), electrocardiograms (ECGs), hematology, chemistry panels (inclusive of expanded markers of liver function, ACTH, Insulin-like Growth Factor-1 (IGF-1) and testosterone concentrations), dipstick urinalysis (microscopic evaluation, if dipstick positive), tumor size by magnetic resonance imaging (MRI) as applicable.

3.3 Exploratory Endpoints

- Proportion of subjects with long-term clinical response to COR-003, defined as mean UFC level ≤ ULN, after 9 and 12 months (Extended Evaluation Phase);

- Proportion of subjects with long-term complete or partial response to COR-003, defined as mean UFC level ≥ 50% reduction from Baseline after 9 and 12 months (Extended Evaluation Phase);

- Change and percentage change from Baseline in mean 24-hour UFC levels after 9 and 12 months (Extended Evaluation Phase);

- Shift in UFC normality categories from Baseline at 9 and 12 months (Extended Evaluation Phase);

- Change and percentage change from Baseline in serum and late night salivary cortisol levels after 9 and 12 months (Extended Evaluation Phase);

- Changes from Baseline in Clinical Signs and Symptoms of CS, on the QoL measures obtained from the Cushing QoL questionnaire, and on the severity of depression obtained from the Beck's Depression Inventory II after 9 and 12 months of dosing (Extended Evaluation Phase);

- Change from Baseline in CS comorbidities biomarkers (HbA1c, SBP, DBP, total cholesterol, LDL, HDL and body weight) after 9 and 12 months of dosing (Extended Evaluation Phase);

- Changes from Baseline for OGTT (pre-diabetics only) and spot albumin/creatinine ratio as a measure of microalbuminuria (only if abnormal at Baseline) after 9 and 12 months of dosing (Extended Evaluation Phase);

- Changes from Baseline for CRP after 9 and 12 months of dosing (Extended Evaluation Phase);

- Clinical benefit rate determined after 1, 2, 3, 4, 5 and 6 months of dosing in the Maintenance Phase and at 9 and 12 months (Extended Evaluation Phase). Clinical benefit is defined as follows:

  1. Clinical response as indicated by UFC ≤ ULN, and
  2. No increase in COR-003 dose during Maintenance Phase, and
  3. A clinically meaningful improvement in any one Baseline CS comorbidity (diabetes, hypertension, hypercholesterolemia, weight) as defined in the Statistical Analysis Plan (SAP), and
  4. No study drug related treatment-emergent adverse event (TEAE) classified as severe or worse.

- Changes in the doses of concomitant medications and in particular anti-diabetic, anti-cholesterol and antihypertensive medications after 6 months of dosing with COR-003 during the Maintenance Phase and during the Extended Evaluation Phase relative to Baseline doses of such medications;

- Changes in the severity score for clinical signs of hypercortisolism obtained from standardized photographs and rated by an adjudication committee after 3 and 6 months of dosing with COR-003 during the Maintenance Phase and at 12 months in the Extended Evaluation Phase.

3.4 Pharmacokinetic Endpoints and Pharmacokinetic/Pharmacodynamic Modeling

- Estimate the following parameters using population PK modeling: 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. 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, will be incorporated into the model.

- Estimate the following pharmacodynamic (PD) parameters: COR-003 concentration producing half-maximal UFC suppression (IC50), the maximal suppression of UFC (Imax) and associated estimates of between subject variability, if feasible. The range of UFC reduction by dose will be explored.

- Other safety and efficacy endpoints will also be explored graphically by dose or summary metrics of exposure.

- The relationship of AESI including QTc interval to dose of COR-003 will be evaluated if data allow.

- The relationship of UFC reduction to dose of COR-003 will be evaluated if data allow.

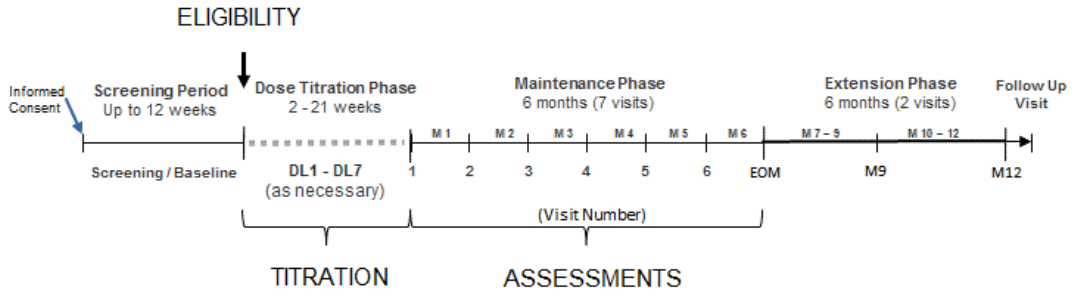
4 STUDY DESIGN

This is a single arm, open label, dose titration study to assess efficacy, safety, tolerability, and PK of COR-003 in subjects with endogenous CS as illustrated in Figure 1. The range of effective doses for COR-003 in this CS population will also be established. Following an initial screening and washout period, as applicable, this study will be conducted in 3 treatment phases as follows:

- **Dose Titration Phase**: approximately 2 to 21 weeks to achieve an effective and tolerable maximum dose (the Therapeutic Dose)—see Section 4.2 for details;
- **Maintenance Phase**: 6 months of treatment at the Therapeutic Dose following the Dose Titration Phase;

- **Extended Evaluation Phase**: 6 months of continued treatment after the Maintenance Phase.

Figure 1 Study Design



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

Blood samples for PK determination will be collected as described in Section 6.2.8.1. Note that the times indicated in the Time and Events Table (Appendix A) are indicative of potential collection times and do not apply to each subject.

Safety data will be collected at the times indicated in the Time and Events Table and as described in Section 6.2. Adequate medical coverage will be provided by the Investigator at all times during the course of 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 on

how to access the medical staff regardless of day and time in order to obtain medical care. An independent Data Safety Monitoring Board (DSMB) will review the safety of the drug throughout the study. At a minimum, the DSMB membership will consist of an endocrinologist with expertise in the treatment and clinical investigation of CS; a gastroenterologist/hepatologist with expertise in the assessment of abnormal LFTs and hepatotoxicity during clinical study conduct; and an expert in the evaluation of QTc interval during clinical study conduct/clinical pharmacologist. The full extent of responsibilities by the DSMB is defined in its charter.

Subjects completing the 6-month Maintenance Phase of the study with COR-003 will remain in the study for an additional 6 months for extended evaluations of safety and efficacy of COR-003 treatment (Extended Evaluation Phase).

At the completion of the 6-month Extended Evaluation Phase, subjects may be eligible to enter an expanded access program and receive continued treatment with COR-003 in accordance with local regulations. If the program is not available at their location, or they are not eligible to participate or do not wish to consent to the program, after completion of the Follow-Up Visit they will be promptly referred back to their endocrinologist (if not the Investigator) for further management according to the local standard of care, and based on their preceding medical history. (Note: As subjects entering the expanded access program for COR-003 will not be discontinuing treatment with COR-003, they will not be required to complete the Follow-Up Visit for this study.)

4.1 Screening Period

After signing the informed consent, subjects will enter the Screening Period. After performing initial Screening assessments, subjects on previous CS medical therapies or other prohibited medications must enter a washout period, as applicable (see Section 5) before completing all Screening assessments detailed in the Time and Events Table (Appendix A). Baseline measurements will be obtained as part of the Screening assessments, after washout and completion of all initial Screening procedures.

If a subject does not initially meet the eligibility requirements described in Section 5, they might be eligible to re-screen but only if their underlying condition has changed in the interim such that they are now likely to meet 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.

4.2 Dose Titration Phase

After confirmation of eligibility at the Baseline Visit, including confirmation of increased UFC levels as per eligibility requirements, each subject will return to the investigational site to receive study medication and will begin dosing at dose level 1 (DL1) with an initial dose of 150 mg twice daily (BID), taken as one tablet in the morning and one tablet in the evening. Decisions for subsequent dose increases will be based on an assessment of each subject's UFC levels and safety data (i.e. tolerability of therapy) and will be made

by the Investigator. The interval between dose adjustments will be approximately 18 days (±4 days)

4.2.1 Dose Titration and Adjustment Criteria

COR-003 will be administered BID according to the titration scheme in Table 1 until **one** of the following criteria has been met:

- Mean 24-hour UFC levels ≤ULN as established for the assay being used at a central laboratory
- Highest protocol-specified dose reached
- Highest tolerated dose reached (in the opinion of the Investigator)

Table 1 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 once daily administered in the evening, except on the day of the in-clinic procedures, when the dose should be administered in the clinic (see Section 8.2.1).

All subjects will be asked to collect two adequate 24-hour urine specimens starting at Day 10 (±1 day) after the start of each dose level, ideally on two consecutive days. The subjects are asked to bring or ship per courier service their two urine collections to the clinic, as soon as possible (approximately Day 12) for measurement of 24-hour UFC levels from each sample. Urine volume and creatinine will be measured as markers of the adequacy of each collection (see Section 6.2.6.1 for definition). Subjects will continue on their current dose of COR-003 until the UFC results have been obtained from the central laboratory (within approximately 2-4 days of shipment). Based on their UFC results and tolerability, subjects will be asked to do **one** of the following:

- Return to the clinic for scheduled assessments and receive the first dose of drug for the next Dose Titration interval;
- Have a confirmatory UFC evaluation (e.g. two additional UFC measurements to determine if the Therapeutic Dose of COR-003 has been reached; Section 4.2.1.1); or
- Enter the Maintenance Phase (if an alternative determination of Therapeutic Dose of COR-003 has been made; Section 4.2.1.1) as applicable.

4.2.1.1 Determination of the Effective and Tolerable Dose of COR-003 (Therapeutic Dose)

When a subject achieves normalized UFC results (≤ULN for UFC) from the mean of the first two adequately collected 24-hour urine samples, two additional 24-hour urine samples will be collected and returned to the clinic for submission to the central laboratory. Subjects should be contacted as soon as the results from the first two 24-hour urine samples are received to ask them to begin the next two 24-hour urine collections.

A Therapeutic Dose for a subject will be considered established when mean UFC levels (determined from a total of four adequate 24-hour urine collections) are ≤ULN of the assay, or the maximum dose allowed has been reached, or a clinically meaningful partial response and the maximal tolerated dose has been reached. Once the Therapeutic Dose has been reached the subject can begin the Maintenance Phase of the study.

Steps for Determination of Therapeutic Dose

- If the mean value for the first two UFC test levels is ≤ULN of the assay of two adequate 24-hour urine collections, the subject should be notified immediately and asked to begin the next two 24-hour urine collections, for the purpose of confirming a biochemical response. The two additional urine collections should be completed and returned to the clinic, as soon as practical (for example, if samples were provided to site on Day 12 following the dose escalation visit and results were received on Day 15, the subject should ideally begin collection the following day (Day 16) and return the two additional samples to the site immediately upon completion of collection (Day 18). The next visit for the subject should be scheduled to coincide with receipt of the results (Day 30 [±7 days]) and the mean of the four UFC test values is available to make the determination of whether or not the Therapeutic Dose has been achieved.
- When confirmatory urine sample collection is required, in order to allow for adequate time for urine sample collection and analysis between visits, the subject should return no later than 37 days after the prior dose escalation visit for either the next dose escalation visit or start of the Maintenance Phase (based on the mean of the four UFC values) [NOTE: Always ensure that the subject has an adequate supply of COR-003 to cover the duration between visits.]
- If the mean value of four adequate 24-hour urine collections is ≤ULN of the assay, the subject may enter the Maintenance Phase at the current dose level (i.e. Therapeutic Dose level) [Section 4.3]. The total duration of the Titration Phase should not be any longer than approximately 21 Weeks; assuming approximately 3 weeks of treatment for each dose level.
- If the mean value of four adequate 24-hour urine collections is >ULN of the assay of four adequate 24-hour urine collections, the subject should proceed to the next Dose Level.

Alternative Determination of Therapeutic Dose

- If the subject has reached the highest <u>allowed</u> dose level and UFC levels remain >ULN of the assay for the mean of two adequate 24-hour urine collections, yet there is

a clinically meaningful partial response from Baseline, the subject may enter the Maintenance Phase at that dose level.
- If the subject has reached the highest tolerated dose and UFC levels remain >ULN of the assay for the mean of two adequate 24-hour urine collections, yet there is a clinically meaningful partial response from Baseline, the subject may enter the Maintenance Phase at that dose level at the discretion of the Investigator.
- If UFC is >ULN and LFTs are elevated, the Investigator may maintain the dose in the Dose Titration Phase in consultation with the Medical Monitor before a decision is made to progress to the next dose level or into Maintenance Phase.

NOTE: If UFC levels remain >ULN of the assay for the mean of two adequate 24-hour urine collections, and there is no clinically meaningful partial response from Baseline upon reaching the highest allowed dose or the highest tolerated dose, discontinuation should be considered. Consultation with the Medical Monitor is encouraged.

4.2.1.2 Dose Titration to the Therapeutic Dose

Subjects will continue the process of dose titration until the Therapeutic Dose has been reached (Section 4.2.1.1).

- If UFC levels are >ULN of the assay for the mean of two adequate 24-hour urine collections, the dose should be increased to the next dose level, unless the highest tolerable dose or the highest protocol-specified dose has already been reached.
- If UFC levels are >ULN of the assay for the mean of two adequate 24-hour urine collections, the subject should return no later than 22 days (18 days ± 4 days) after the prior dose escalation visit for the next dose escalation visit.

Other factors that are to be considered during the Dose Titration Phase:

- Subjects will have ECG evaluations at Baseline and within approximately 1 to 2 hours after drug administration (i.e., at ~ Cmax) during the Dose Titration Phase at each dose level), monthly (at the Therapeutic Dose) during the Maintenance Phase and at each visit during the Extended Evaluation Phase using the Spaulding ECG device for collection of up to 5 minutes of continuous ECG (Section 6.2.4). The dose of study medication will be reduced if the confirmed COR-003-related QTc interval persistently increases to >500 msec or >60 msec from Baseline. Please refer to Section 5.3.1 where guidance to the Investigator on the assessment of the prolonged QTc interval is provided in detail.

- If the subject develops signs and/or symptoms of adrenal insufficiency (e.g., orthostatic hypotension, nausea, vomiting, abdominal pain), based on further investigation (see Section 6.3.3) and clinical judgment, the Investigator may temporarily stop dosing of the study medication to allow resolution of these symptoms. In such cases, at the discretion of the Investigator, the dose will be reduced and restarted at a preceding dose level (see Section 6.2.4.2). In the event that this observation is made at DL1, the subjects may receive a lower dose of **150 mg once daily (DL0)** based on the medical discretion of the Investigator and agreement with the Sponsor. Subjects may resume the Dose Titration scheme after a dose

reduction at the discretion of the Investigator and agreement with the Sponsor. See Section 6.3.3 for details on assessment of signs and symptoms of adrenal insufficiency.

4.2.2 Dose Titration Above 600 Mg Total Daily Dose

COR-003 has only been dosed up to 600 mg/day in diabetic subjects. The safety in subjects at doses beyond 600 mg/day is unknown. For this reason, subjects that reach total daily doses of > 600 mg/day (i.e., doses of 750, 900, 1050, and 1200 mg/day) must be monitored more closely in order to ensure proper evaluation of the safety of doses at these levels. In addition to the assessments that will be carried out during dose escalation for doses ≤600 mg/day, for each dose escalation beyond 600 mg/day, subjects will be asked to return for one additional safety evaluation 7 days (±3 days) after each dose escalation to include the following assessments: AEs, vital signs, routine safety laboratory assessments (including LFTs), ECGs, and morning serum cortisol levels as outlined in Time and Events Table (Appendix A). Subjects will be advised to contact the Investigator immediately in the event of developing adrenal insufficiency (see Section 6.3) or other AEs at any time.

- Return 7 days (±3 days) after each dose level escalation visit for DL4 through DL7 for additional safety assessment (see Section 6.2.7.1);
- Start the collection of two adequate 24-hour urine samples 10 days (±1 day) after the dose level escalation visit for DL4 through DL7 - provide containers to sites as soon as possible after completion (approximately 12 days after dose level escalation);
- If the mean value for the first two adequate 24-hour urine collections is >ULN of the assay, the subject should return no later than 22 days (18 days ± 4 days) after the prior dose escalation visit for next dose escalation visit;
- If the mean value for the first two adequate 24-hour urine collections is ≤ULN of the assay and additional UFC tests are needed to confirm the mean value of ≤ULN, the subject should be notified to collect an additional two 24-hour urine samples and return them to the site, as soon as possible after completion (see timing details in Section 4.2.1.1).

The results of relevant assessments should be available promptly in order for the Investigator to make decisions for the safety of the subject. Reports of Serious Adverse Events (SAEs) experienced at these higher doses will be shared with all Investigators regularly during the study.

4.3 Maintenance Phase

By convention, the very first visit during the Maintenance Phase will be called “Month 1” and will take place on the first day of Month 1 of the Maintenance Phase. After the Month 1 visit, subjects will be asked to return to the clinic monthly (every 30 ± 7 days) for approximately 6 months for assessment of efficacy and safety (as outlined in the Time and Events Table [Appendix A]).

During the Maintenance Phase, doses may not be increased to maintain UFC levels at or below ULN of the assay unless it is confirmed that a dose increase is deemed medically necessary, based on a totality of evidence including other disease markers or symptoms, at the discretion of the Investigator after discussion with the Medical Monitor. The reason for this restriction is that some variability in mean UFC levels from two urine collections is expected, and such variability in and of itself is not considered a sufficient reason for further dosage adjustment. If it is deemed medically necessary, prior to increasing the dose during the Maintenance Phase, two additional adequate 24-hour urine collections should be obtained within 2 weeks of the first UFC samples to provide a total of four UFC samples for analysis. If confirmed hypercortisolemia is present, the COR-003 dose may be increased by 150-mg increments as medically indicated up to the maximally allowed dose of 1200 mg/day, and the subject may stay in the study through completion.

During the Maintenance Phase the COR-003 dose may also be reduced temporarily or permanently for safety reasons, including but not limited to LFT elevation (see Section 5.3.2, instructions for re-challenge), QTc prolongation (Section 5.3.1) and adrenal insufficiency (Section 6.3.3). If medically indicated, the dose should be resumed at the individual's Therapeutic Dose. **All dose adjustments during the Maintenance Phase must be documented.**

4.4 Transition from Maintenance Phase to Extended Evaluation Phase

Prior to the End of Maintenance Phase Visit, four complete 24-hour urine collections will be obtained and subjects may enter the Extended Evaluation Phase (Section 4.5).

4.4.1 Exclusion of Treatment Effect Due to Delayed Onset of Radiation Therapy

Previously irradiated subjects must stop treatment with COR-003 for at least 2 weeks after the end of the 6-month Maintenance Phase (End of Maintenance Phase Visit) and provide four complete 24-hour urine collections for UFC measurements collected at least 14 days following the End of Maintenance Phase Visit. If the 24-hour UFC results indicate that UFC levels are elevated, the subject may subsequently restart therapy and continue into the Extended Evaluation Phase, at the discretion of the Investigator (Section 4.5). [NOTE: Subjects restarting therapy should initiate therapy as soon as the need is identified and should return for their next in-clinic visit (M9) for study assessments and resupply of study medication 90 days (±14 days) from the End of Maintenance Visit.]

4.5 Extended Evaluation Phase

The end of the Maintenance Phase visit will be the start of the Extended Evaluation Phase. In the 6-month Extended Evaluation Phase, subjects will return to the clinical site every 3 months (every 90 days ± 14 days) for assessments, (i.e., at the end of Months 9 and 12), and will have safety and efficacy evaluations as indicated in the Time and Events Table (Appendix A).

After completion of treatment in this study, if subjects do not extend treatment through the expanded access program (Section 4.7), they will return for a Follow-Up Visit as indicated in the Time and Events Table (Appendix A). The Follow-Up Visit should be a minimum of 2 weeks (14 days) and no longer than 30 days following the completion of treatment. [NOTE: The Follow-Up Visit is not required for subjects continuing into expanded access treatment (see Section 4.7)].

4.6 Stopping Criteria

Dosing with the study medication will cease 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 any clinically relevant response at the maximally tolerated dose, in the opinion of the Investigator
- QTc prolongation as specified in Section 5.3.1 at 150 mg/day
- LFT abnormalities as specified in Section 5.3.2
- Adrenal insufficiency at the lowest dose of COR-003 (150 mg daily)—See also Section 6.3.3 for more details
- Any withdrawal criteria specified in Section 5.3.

Subjects who are withdrawn early will complete the Follow-Up Visit (see Appendix A) and provide two adequate 24-hour urine collections within approximately 2 weeks of termination of treatment with COR-003.

The cause for withdrawal will be documented and appropriately captured in the database. Withdrawn subjects, due to any of the above criteria, must receive appropriate follow-up medical care. The Investigator will explain all other treatment options available to them in their country of residence and subjects will be promptly referred back to their endocrinologist (if not the Investigator) for further management according to the local standard of care and based on their preceding medical history.

4.7 Optional Expanded Access Program

An expanded access program (COR-2015-EAP) will be made available, as local regulations allow, to sites participating in this study. Subject interest and eligibility for participating in the expanded access program will be evaluated at the M9 visit, including the informed consent process. If eligible, they will begin participation in the COR-2015-EAP program upon completion of the M12 visit. Subjects continuing into expanded access program will NOT be required to complete the Follow-Up Visit for COR-2012-01.

If a subject completing COR-2012-01 at a site that does not have regulatory approval to provide access to COR-003 under the expanded access program wishes to continue COR-003 treatment after completing this study, Cortendo will make a reasonable effort to provide continued access to the medication through another access option that meets all applicable local and national regulatory requirements.

In the event that continued access to COR-003 is anticipated but delayed for any reason, and dosing with COR-003 will be interrupted for more than 2 weeks, the Follow-Up Visit should occur according to the Time and Event Schedule (see Appendix A).

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

Subjects eligible for enrollment in the study must meet all of the following criteria:

1. Male or female ≥18 years of age
2. Able to provide written informed consent prior to any study procedures being performed; eligible subjects must be able to understand the informed consent form prior to inclusion into the study.
3. Confirmed diagnosis of newly diagnosed, persistent or recurrent CD or endogenous CS of other etiology if subjects are not candidates for surgery or radiotherapy within the 18 months after enrollment.

   Previous medical records will be collected and used to support the diagnosis of CD or endogenous CS of other etiology, including the following etiologies:

   - Ectopic ACTH secretion, i.e. ACTH not of pituitary origin
   - Ectopic corticotropin-releasing hormone (CRH) secretion
   - Adrenal-dependent CS (i.e. adrenal adenoma (NOT carcinoma), adrenal hyperplasia, etc.)
   - Etiology unknown

   In the absence of pathological or post-surgical confirmation of the diagnosis of CD (i.e. documented adrenal insufficiency post-adenomectomy or hypophysectomy, which will be considered diagnostic). The following historical evidence will be considered satisfactory to establish the diagnosis of CD:

   - **Plasma corticotropin** (ACTH) level >20 pg/mL (4.5 pmol/L) or greater (Note: ACTH ≥5 pg/mL (1.1 pmol/L) and ≤20 pg/mL will generally suffice only if accompanied by either a positive CRH stimulation test or DST or combined CRH-DST) **PLUS** one of the diagnostic strategies described below based on pituitary MRI/computed tomography (CT) findings (Note: pituitary imaging preceding the original diagnosis is a requirement for eligibility):
   - **For tumors ≥6 mm** by imaging:
     - Inferior petrosal sinus sampled (IPSS) ACTH central:plasma gradient ≥2 before CRH or ≥3 after CRH, OR if IPSS was not done then:
     - Positive ACTH and/or cortisol response to CRH/desmopressin or combined CRH-desmopressin stimulation **plus** high-dose (8 mg)

dexamethasone suppression of plasma cortisol, ideally on more than one occasion, performed and interpreted according to internationally recognized standards of diagnosis

- In the absence of IPPS and the combination of tests described, 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.

- **For tumors <6 mm** or not visible by MRI:
  - IPSS with ACTH central:plasma gradient ≥2 before CRH or ≥3 after CRH
  - 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. Regardless of the etiology of endogenous CS, subjects MUST have elevated mean 24-hour UFC levels ≥1.5X ULN based on the normative range of the central lab assay and on a minimum of four measurements from adequately collected urine. Urine will ideally be collected on sequential days.
5. In addition to elevated mean UFC, presence of abnormal values from **one** of the following tests:
   - Abnormal DST: Elevated 8 AM serum cortisol ≥1.8 μg/dL (50 nmol/L) after 1 mg dexamethasone orally at 11 PM the evening prior (if not conducted already in the diagnostic workup of the subject within the previous 2 months before start of Screening Phase; in that case previous test results and details of conduct will need to be available by the Baseline Visit)
   - Elevated late night salivary cortisol concentrations (at least two measurements) >ULN

   NOTE: For subjects with estimated glomerular filtration rate (eGFR as determined by Modified Diet in Renal Disease MDRD equation) >40 and <60 mL/min/1.73 m^2 in addition to meeting the UFC criteria, late night salivary cortisol test results (≥2 measurements) **MUST** also demonstrate evidence of CS.
6. Previously irradiated subjects with CD or endogenous CS of other etiology will be allowed as long as the radiation treatment occurred >4 years ago and subjects have not exhibited evidence for improvement in their underlying CD for 6 months prior to the Screening visit. The total number of previously irradiated subjects enrolled in this study will not exceed 10.
7. Subjects with CD or CS of other etiology who are not candidates for surgery, refuse surgery, or in whom surgery will be delayed for at least 18 months following enrollment. Subjects may be allowed to participate in the trial while awaiting surgery, but must agree to complete this study prior to surgery. For subjects who have already

undergone surgery, a minimum of 6 weeks should have elapsed before the subject can be deemed a surgical failure. Subjects who have undergone surgery should be stable post-surgery (i.e., no significant post-operative sequelae remain and the risk of such sequelae is considered negligible).

8. Subjects on treatment for CD or endogenous CS of other etiology for whom treatment has been inadequate or not well tolerated must agree to the following minimum washout periods prior to the Baseline Visit:

    - 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

9. Subjects on megestrol acetate or medroxyprogesterone acetate (and selected other synthetic progestins) must agree to a washout period of at least 6 weeks prior to the Baseline Visit

10. A female is eligible to enter and participate in the study if she is of:

    Non-child bearing potential (i.e. physiologically incapable of becoming pregnant, including any female who is post-menopausal or surgically sterile). Surgically sterile females are defined as those with a documented hysterectomy and/or bilateral oophorectomy or tubal ligation.
    Post-menopausal females are defined as being amenorrheic for greater than 1 year with an appropriate clinical profile, e.g. age > 45 years, in the absence of hormone replacement therapy. However, in questionable cases, a blood sample with follicle stimulating hormone (FSH) > 40MIU/ml and estradiol < 40pg/ml (<140 pmol/L) is confirmatory.

    OR

    Child-bearing potential and agrees to use highly effective methods of birth control while participating in the study and for 2 weeks after the study is completed (see Section 6.2.5.1).

11. Fertile men must also agree to use a medically acceptable form of birth control while on study drug and up to 2 weeks after the study is completed (see Section 6.2.5.1).

12. Able to comprehend and comply with procedures.

5.2 Exclusion Criteria

Subjects will be excluded from the study if any of the following criteria are met:

1. Subjects with Pseudo-Cushing's syndrome based on assessment of the Investigator. Appendix G describes a number of conditions in which elevated cortisol levels may be observed in the absence of CS, sometimes referred to as Pseudo-Cushing's syndrome
2. Subjects with cyclic CS based on assessment of the Investigator

3. Subjects with a non-endogenous source of hypercortisolism such as exogenous source of glucocorticoids or therapeutic use of ACTH.
4. Known inherited syndrome as the cause of hypercortisolism, including but not limited to multiple endocrine neoplasia Type 1, McCune Albright Syndrome and Carney Complex
5. Subjects with adrenal carcinoma
6. History of malignancy, other than thyroid, early stage prostate, squamous cell and basal cell carcinoma, within 3 years prior to the Screening Phase. Subjects with history of such allowed carcinoma must have a life expectancy of >18 months and must be considered medically stable. Subjects with early stage prostate cancer undergoing no treatment due to low grade potential may be enrolled.
7. Clinical or radiological signs of compression of the optic chiasm.
8. Major surgery within 1 month prior to enrollment (informed consent form signing).
9. Subjects with clinically significant abnormality in 12-lead ECGs during the Screening Phase needing medical intervention.
10. Subjects with QTc interval of >470 msec during the Screening Phase.
11. Subjects with a history of Torsades des Pointes, or ventricular tachycardia, or ventricular fibrillation, or history of prolonged QT syndrome (including family history), or use of medications resulting in QT/QTc prolongation, or hypokalemia <3.0 meq/L.
12. Pre-existing hepatic disease; subjects with mild to moderate hepatic steatosis consistent with fatty infiltration (non-alcoholic fatty liver disease [NAFLD] are allowed).
13. Positive for hepatitis B surface antigen (HbsAg) or positive hepatitis C test.
14. History or symptoms of recurrent symptomatic cholelithiasis or pancreatitis.
15. LFTs must not be above the following cut-offs during the Screening Phase:
    - ALT and/or AST >3 X ULN
    - Total bilirubin (TBN) >2 X ULN

    If all LFTs are within normal limits (WNL) and TBN is elevated, examination of direct and indirect bilirubin may be conducted. Subjects with isolated indirect TBN up to 3X ULN are presumed to have Gilbert's syndrome and may be enrolled if all other LFTs are within normal levels.
16. History of documented or suspected drug-induced liver injury requiring drug discontinuation of ketoconazole or any azole antifungals.
17. Pregnant or lactating women
18. Human immunodeficiency virus (HIV)-positive.
19. History of persistent uncontrolled hypertension (>180/120 mmHg) despite medical intervention.
20. Subjects with hypercholesterolemia who are currently treated with atorvastatin, lovastatin or simvastatin and not willing or unable to change to alternative therapies, i.e. pravastatin, fluvastatin, or rosuvastatin within 2 weeks of start of the Screening Phase.

21. Body habitus preventing repeated venipuncture as required by protocol.
22. Subject is currently in another study or has received any investigational treatment (drug, biological agent or device) within 30 days or five half-lives of treatment, whichever is longer.
23. Repeated hospitalization for hyperglycemia or for any complication of hyperglycemia and diabetes during the last 12 months
24. Subjects with decreased renal function as defined by eGFR <40 mL/min/1.73 m^2, using MDRD equation.
25. 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 to perform the necessary procedures (for example, psychiatric instability or severe disability).
26. Abnormal free thyroxine (T4). Subjects with thyroid stimulation hormone (TSH) below the lower limit of normal (<LLN) and normal free T4 are permitted to participate in the study.
27. Subjects who have a history of alcohol or drug abuse in the 6-month period prior to enrollment.
28. Subjects who have been treated with mitotane within 6 months of the Screening Phase.
29. Subjects who are currently taking any H2 receptor antagonists, proton-pump inhibitors, or sucralfate (all of which inhibit absorption of COR-003). A list of orally acceptable antacids (for example, Mylanta and Maalox) will be provided, and can only be taken a minimum of 2 hours **after** dosing of COR-003.
30. Subjects who receive any prohibited concomitant medication and cannot discontinue it safely prior to the Baseline Visit. Section 10 and Appendix J provide more complete lists of specific medications that are not permitted to be used during this study. Below is a partial listing of prohibited medications:
    - Weight loss medications (prescription or over the counter);
    - Acetaminophen (paracetamol) >3 g total daily dose;
    - Strong **inducers** or **inhibitors** of CYP3A4 enzyme system that may interfere with the metabolism of COR-003 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 might pose unacceptable risks due to overlapping toxicities (e.g. QT prolongation, liver toxicity);
    - Genuine licorice.

5.3 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 5.3.1 and 5.3.2, either at the discretion of the Investigator or at the subject's request (see also Section 4.6, Stopping Criteria).
- 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 case report forms [CRFs] and decide, in accordance with the Sponsor, whether the subject is to be withdrawn).

All premature discontinuations and their causes must be carefully documented by the Investigator on the CRF, and, if need be, on the AE page.

If, for any reason, a subject is withdrawn before completing the study, the reason for termination will be entered in the CRF. All data gathered on the subject prior to termination will be made available to the Sponsor. All withdrawn subjects will be asked to report to the clinic for a Follow-Up Visit at approximately 2 weeks after receiving their last dose of the study medication. All assessments at the Follow-Up Visit are listed in the Time and Events Table (Appendix A). All AEs will be followed until resolution or at a minimum of 30 days after the last dose of the study medication.

5.3.1 Withdrawal due QTc Interval Prolongation

If a persistent and confirmed COR-003-related QTc interval prolongation >500 msec or a change from Baseline of >60 msec as defined below is identified, an attempt should be made to manage such QTc prolongations by dose reduction. If a persistent and confirmed COR-003-related QTc interval prolongation >500 msec or a change from Baseline of >60 msec is observed at the lowest COR-003 dose (150 mg/day), administration of the study drug will cease and the subject will be withdrawn.

In order to decide whether a QTc prolongation is persistent and confirmed to be related to COR-003, QTc will be evaluated using the Spaulding ECG device or a local ECG device with central reading of the ECG by Spaulding. The Investigator should consider alternative possibilities as causative or contributory to QTc prolongation prior to discontinuation of COR-003, including concomitant medications that may result in prolongation of the QTc interval either directly or through interference with the metabolism of COR-003, recent food ingestion (temporary QTc elevation), and electrolyte abnormalities (particularly serum calcium, magnesium and potassium). Interfering concomitant medications with QT prolongation potential are contraindicated in co-administration with COR-003 and must be stopped (Section 10.2). Please also see Section 6.2.4.1 for guidance on the assessment of QTc interval prolongation. Regardless of seriousness or causality, instances of persistent QTc prolongation should be reported to the Sponsor's designated Pharmacovigilance group within 24 hours from the time the

persistent prolongation has been confirmed, in the same manner as SAEs (see Section 13.2.2).

If persistent and confirmed QTc prolongation, as defined above, is observed, an additional PK sample should be collected as close to the time of the event as possible, ideally within several hours of dosing.

5.3.2 Withdrawal and/or Re-Challenge due to Liver Function Tests (LFTs)

The recommendations within the Food and Drug Administration (FDA) Guidance on Drug-Induced Liver Injury: Premarketing Clinical Evaluation (May 2009) have been adopted for use in this protocol to address abnormal LFTs. LFTs will be measured at every study visit. In addition, LFTs will be measured immediately if subjects develop signs and symptoms suggestive of hepatic dysfunction (any of the following: nausea, anorexia, fever, fatigue, right upper quadrant discomfort, pruritus, dark urine or acholic stool). **Nausea, anorexia, and fatigue are non-specific symptoms and may be caused by hypocortisolemia; however, appropriate medical evaluation of such symptoms must include assessment of LFTs.** Other testing including laboratory assessments to assess causality (such as, hepatitis [A, B, C, E], autoimmunity), imaging and consultation with a liver specialist should be obtained prior to a planned withdrawal of the subject due to elevated LFTs. Appropriate medical evaluations and interventions should be implemented based on the clinical presentation of the subject, including appropriate diagnostic imaging procedures. All such medical interventions will be recorded in the CRF. While LFTs may be assayed at a local lab for immediate medical intervention, simultaneous samples **must** be sent to the central laboratory to ensure consistency of assay and interpretation.

Subjects withdrawn due to LFT abnormalities must be followed until LFT normalization or until near Baseline values and stable. Subjects not withdrawn from the study may be re-challenged after resolution of LFT abnormalities, at the discretion of the Investigator **AND** with approval by the Cortendo Medical Monitor.

In agreement with FDA Guidance of 2009, discontinuation of therapy should be considered if:

- ALT or AST >8X ULN
- ALT or AST rises to >5X ULN in <4 weeks or persists for >2 weeks
- ALT or AST >3X ULN **and** TBN >2X ULN or International Normalized Ratio (INR) >1.5 not explained by any other cause such as viral hepatitis, and without evidence of cholestasis
- ALT or AST >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 >3X ULN and/or AP >2X ULN, and/or TBN >2X ULN in the absence of evidence for obstruction or Gilbert

syndrome. An ultrasound evaluation of the gallbladder and bile duct should be conducted to exclude cholestasis as the cause for elevated AP and/or TBN.

Subjects with ALT and/or AST >3X ULN or AP >2X ULN (in the absence of evidence for cholestasis) or TBN >2X ULN (in the absence of evidence for cholestasis and except for subjects enrolled with presumed Gilbert's syndrome) at any visit will undergo serial repeat LFT and INR evaluations. The first repeat LFT should occur as soon as possible after initial determination to confirm the observation and thereafter at 3 to 4 day intervals or as the clinical situation dictates. Appropriate medical evaluations and interventions should be implemented based on the clinical presentation of the subject.

If the LFTs return towards Baseline, serial measurements can be discontinued at the discretion of the Investigator, and the subject will continue for the remainder of the trial. If therapy has been interrupted and LFTs have normalized, subjects may be re-challenged at the discretion of the Investigator AND with approval by the Cortendo Medical Monitor. If LFT elevations persist beyond 4 weeks after interruption of therapy or demonstrate a trend of worsening following interruption, then the subject should be withdrawn from the study. The subject will continue to be followed after withdrawal until resolution or normalization of the laboratory abnormality that resulted in the withdrawal.

If on serial measurements and in the absence of clinical signs or symptoms, the ALT and/or AST continue to rise (but TBN do not exceed the cut-offs for study drug cessation/early termination), subjects will continue on study drug and protocol unless the ALT and/or AST levels are >8X or are persistently higher than 5X ULN. If the ALT and/or AST levels exceed these levels, the subject should stop taking the study medication immediately.

6 STUDY ASSESSMENTS AND PROCEDURES

The exact timings of each assessment are provided in the Time and Events Table (Appendix A). Detailed procedures are provided in the Study Procedures Manual. The study is being conducted 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 according to standard of care, at the discretion of the Investigator. Changes to the medical conditions, history and medications and all other medical interventions will be documented in the CRFs as unscheduled visits.

The study will consist of the following phases with approximate timings:

- Screening Phase (up to approximately 12 weeks' duration, prior to first dose)
- Dose Titration Phase (approximately 2-21 weeks' duration)
- Maintenance Phase (6 months' duration)
- Extended Evaluation Phase (6 months' duration)

After signing the informed consent, subjects will enter the Screening Phase. After performing the initial Screening assessments, subjects on previous CS therapies must enter a washout period, as applicable (see Section 5.1) before completing all Screening assessments detailed in the Time and Events Table (Appendix A). Baseline evaluations 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 5.1), if applicable. Results from the Baseline assessments are necessary in order to determine if the subject remains eligible for participation in the study. Please see the Study Procedure Manual (SPM) for details on urine collections.

All subjects must meet all eligibility criteria prior to the first dosing.

A screen failure subject is one from whom a signed informed consent is obtained but who has not started on treatment and failed to meet some or all eligibility criteria at Baseline.

With approval by the Sponsor Medical Monitor, subjects may have repeated assessments of laboratory values for screening purposes to confirm eligibility if the condition limiting their participation has changed and is no longer limiting. Re-screening is allowed for subjects with changes in their medical condition that alters their potential to meet the eligibility criteria. All re-screenings are considered exceptional and require prior permission of the Medical Monitor.

6.1 Demographic/Medical History Assessments

The following demographic parameters 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 5.1 and will include the following, as available:

- An effort will be made to collect the following information for documentation of medical history as part of this study:
    - Documentation of diagnosis of CS, including but not limited to evaluations for CS for the previous 6 months, e.g., levels of UFC, late night salivary and/or serum cortisol, DST results, IPSS results and diagnostic imaging results

  - Documentation of associated metabolic complications (e.g., diabetes, hypertension, osteoporosis, and reproductive dysfunction)
  - Documentation of prior management of CS for the previous 3 months, including medications (capturing doses, duration of treatment, time of discontinuation and reason for discontinuation of medication) and any surgical or radiation therapies

- Available clinical laboratory data for the previous 3 months; specifically: LFTs (ALT, AST, AP, direct and TBN), HbA1c, fasting serum glucose, OGTT, serum lipid panel (LDL-C, HDL-C, total cholesterol, triglycerides), CRP, urinary albumin/creatinine ratio, testosterone and IGF-1 concentrations
- Available blood pressure data for the previous 3 months
- Medication history (all medications, including any non-prescription medications, other than those to treat CS specifically) taken within 3 months prior to Screening with particular attention to blood pressure, anti-diabetic and cholesterol lowering drugs
- History of drug and alcohol use.

6.2 Safety and Efficacy Assessments

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

Full physical examinations will be performed by a physician at the times indicated in the Time and Events Table (Appendix A). The physical examinations will be inclusive of all body systems, and should include height (cm) and weight (kg). Abdominal girth will be measured in triplicate at the times indicated in the Time and Events Table and as described in the SPM. BMI will be calculated based on data entered into the CRF during that visit.

The examining physician will be asked to complete a questionnaire related to the assessment of Clinical Signs and Symptoms of CS (see Appendix M). The results will be used to quantify changes in Clinical Signs and Symptoms of CS. Details regarding these assessments will be provided in the SPM.

6.2.2 Standard Photographs

Standard photographs will be taken for consenting subjects to document visible signs of hypercortisolism at the times indicated in the Time and Events Table (Appendix A) as described in the COR-2012-01 Photography Manual.

6.2.3 Vital Signs

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

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

- Use of an appropriately sized cuff for the size of the subject's arm circumference should be utilized to minimize inaccurate readings. The sites may use available cuffs on site for these measurements.
- No smoking or exercise for at least 30 minutes before a blood pressure measurement.
- Subjects should sit in a chair with a back support and the arm supported at heart level with feet flat on the floor. The subject should void prior to the measurement.
- Blood pressure measurements will be measured in triplicate over a minimum of approximately 10 minutes after the subject has rested in a sitting position for at least 10 minutes. The three measurements will each be recorded in the CRF and a mean value for that visit will be calculated for reporting.

Vital sign measurements must be repeated if clinically significant or machine/equipment errors occur. Out of range blood pressure or HR measurements will be repeated at the Investigator's discretion. Any confirmed, clinically significant change from Baseline vital sign measurements must be recorded as AEs.

Guidelines for classification for blood pressure levels and recommendations for follow-up are provided in Appendix I.

6.2.4 12-Lead Electrocardiograms (ECG)

Male patients with CS have been reported to have prolongation of the QT interval [Giraldi 2011]. Thus, the inclusion criteria have allowed for this possibility and both males and females with QTc prolongation will be allowed into the study with Baseline QTc ≤470 msec.

QTc interval is highly variable during the course of a day. Food intake can increase QTc intervals. Nausea, vomiting, upset stomach, and dizziness can also cause prolongation in the QTc interval, as well as electrolyte abnormalities (low serum magnesium, calcium and potassium levels).

Many drugs can prolong the QTc interval directly, or in the case of COR-003, through interference with the metabolism of COR-003 causing levels of the drug to increase, thus resulting in a prolongation of the QTc.

In this study, ECG monitoring is being performed at the designated times (as in the Time and Events Table in Appendix A), ideally using the Spaulding ECG device continuously for a maximum of 5 minutes.

It will be upon this integrated summary result that QTc prolongation will initially be identified. The integrated summary of the ECG assessments (including arrhythmia analysis) will be done centrally after electronic transmission of the data, along with real-time results provided to the Investigator.

NOTE: ECGs during the Screening Visit (single ECGs) are not required to be performed using the Spaulding ECG device. The Spaulding ECG device should be used at the Baseline Visit and for all subsequent assessments during the study. In the event that the

Spaulding ECG device is not available, a local ECG may be performed (following the below guidance) and transmitted to Spaulding via a paper printout of the recording.

ECGs will be obtained within approximately 1 to 2 hours after drug administration (i.e., at approximately Cmax of COR-003). ECGs will be obtained after the subject has rested in a supine position for at least 5 minutes, and should be conducted after the subject has not eaten for at least 2 hours. A small snack will be allowed for diabetic subjects and subjects who are intolerant of fasting since food intake can prolong QTc intervals. Food intake has to be recorded in the CRF. The recording from the continuous ECG (maximum of 5 minutes) reading with the Spaulding device will be uploaded electronically to a computer and subsequently transmitted over the internet for centralized analysis and archiving. The system will provide automated measurements of HR, respiratory rate (RR), PR, QRS, QT, QTcF and QTcB and ECG diagnostic statements to the investigative site within a short time following the completion and uploading of the recording. A central reader cardiologist, not involved in the conduct of the study, will subsequently evaluate the ECGs. **It is imperative that the transmission of all ECGs to the central reader takes place as soon as possible after the completion of the test to allow for the proper medical evaluation of the subject should QTc prolongations occur**.

6.2.4.1 Prolongation of QTc Interval > 500 Msec or > 60 Msec Above Baseline

The potential risk of protracted, drug-induced 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 at least >500 msec or >60 msec above Baseline.

Subjects with prolonged QTc intervals >500 msec or >60 msec increase over the QTc interval at the Baseline Visit based on the assessment ideally using the Spaulding ECG device or local ECG must be medically observed until the QTc has returned to a value ≤500 msec or ≤60 msec change from Baseline.

The following need to be considered in cases of QTc prolongation:

- If the integrated ECG reading demonstrates a QTc prolongation >60 msec from Baseline or an absolute QTc >500 msec, the subject should 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.

- The subject should also be questioned about the use of any other medications that may have increased QTc interval, either directly because of their direct effect on the QTc interval or indirectly as a result of a drug interaction that may have increased the concentrations of COR-003. If such a drug is identified, it should be stopped immediately.

- The subject should be evaluated for symptoms of nausea or recent vomiting prior to the ECG assessment, lightheadedness or other symptoms that may influence the QTc interval. In such cases, the ECG evaluation should be conducted once the subject's symptoms have abated. COR-003 dosing 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, 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 QTc prolongation >60 msec above Baseline or an absolute value of >500 msec, a blood sample should be obtained from the subject for evaluation of electrolyte abnormalities, including potassium, magnesium and calcium concentrations in addition to routine electrolytes and for a PK evaluation. If electrolyte abnormalities are identified, these should be corrected before re-evaluation of the ECG. COR-003 may be temporarily withheld until electrolytes can be normalized.

If electrolytes are normal and no other cause can be identified to account for the absolute QTc interval >500 msec (or >60 msec above Baseline), and the ECG evaluation on repeat determination demonstrated persistent QTc prolongation, causal relationship to COR-003 should be assumed and COR-003 should be withheld. The ECG should be monitored per discretion of the Investigator until resolution of the QTc prolongation. In all cases, abnormal morphology of the ECG (especially T wave changes), if present, will be recorded in the CRF.

If the subject is on the lowest possible dose of COR-003 (150 mg/day) and has persistent and COR-003-related QTc interval prolongation >500 msec or a change from Baseline of >60 msec, administration of the study drug will cease permanently and the subject will be withdrawn**.**

At higher doses, an attempt should be made to manage persistent QTc prolongations that are deemed to be related to COR-003 by resuming treatment at a lower dose after resolution of QTc prolongation as described below. 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 several hours of dosing.

Persistent and confirmed QTc prolongation are defined as follows:

- Persistence: The 12-lead ECG should be repeated within 30 minutes of the first ECG revealing a QTc prolongation to confirm the persistent reading.
- Confirmation: The Investigator should consider alternative possibilities as causative or contributory to the QTc prolongation prior to discontinuation of the

study drug and/or study withdrawal. Such contributing factors include nausea/vomiting, concomitant medications that may result in prolongation of the QTc interval either directly or through interference with the metabolism of COR-003, recent food ingestion (temporary QTc elevation), and electrolyte abnormalities (particularly serum calcium, magnesium and potassium). Supplementing potassium to raise serum potassium into the high-normal range can shorten the QTc interval in many cases. Interfering concomitant medications with this potential are contraindicated in co-administration with the study drug and must be stopped (Appendix J).

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

6.2.4.2 Resuming Treatment After Resolution of QTc Prolongation

COR-003 at a lower dose can be restarted after a washout period of 2 days and resolution of the QTc prolongation (absolute QTc interval ≤500 msec or is ≤60 msec above Baseline). After restart, ECG evaluation should occur within 1 to 2 hours of resumption of dosing and be continued according to the visit schedule for increased safety monitoring.

Abnormal morphology of the ECG (especially T wave changes), if present, will be recorded in the CRF. If the absolute QTc interval remains ≤500 msec, or remains ≤60 msec below the Baseline value, administration of COR-003 may be continued at the discretion of the Investigator and with approval by the Cortendo Medical Monitor.

If persistent QTc prolongation deemed related to COR-003 is observed after reintroduction at a lower dose, COR-003 should be permanently discontinued (see Withdrawal criteria in Section 5.3.1), an additional PK sample should be collected as close to the time of the event as possible and repeat ECG evaluation should occur until QTc interval remains ≤500 msec, or ≤60 msec below the Baseline value.

6.2.5 Clinical Laboratory Tests

Samples for clinical laboratory testing will be collected at the times indicated in the Time and Events Table (Appendix A). A complete list of all the analytes, including an entire battery of LFTs, is provided in Appendix B. In addition to biochemistry, hematology and urinalysis, laboratory parameters will also include the following: serum cortisol, ACTH, FSH (women only), TSH, free T4, serum free and total testosterone, IGF-1, coagulation parameters (prothrombin time [PT], partial thromboplastin time [PTT], INR), triglycerides, serum lipid panel, HbA1c, CRP, and spot urine for albumin/creatinine ratio to determine microalbuminuria. Screening safety laboratory tests will also include the following: HIV, as well as antibody for hepatitis B and C. All testing will be conducted in a fasting state and in the morning unless stated differently in the Time and Events Table (Appendix A).

TSH and free T4 will be measured during the Screening Phase, DL4 during the Dose Titration Phase, then every 2 months during the Maintenance Phase and both Extended Evaluation Phase visits. If subjects achieve their maximum COR-003 dose prior to DL4, their TSH and free T4 levels must be measured at Month 1 of the Maintenance Phase (time = 0), every 2 months during the Maintenance Phase and every 3 months during the Extended Evaluation Phase.

6.2.5.1 Pregnancy

Regardless of post-menopausal status, all female participants must have a negative pregnancy test at screening and at study visits indicated in the Time and Events Table (Appendix A). A urine βhCG will be performed at the first Screening visit and all other subsequent visits. Results of the test must be available before dosing can begin.

Post-menopausal females will be defined as having amenorrhea for a minimum of 24 consecutive months and an elevated FSH level during the Screening Phase.

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
- Implants of levonorgestrol inserted for at least 1 month prior to the study medication administration but not beyond the third successive year following insertion; or
- Oral contraceptive (combined or progestogen only) administered for at least one monthly cycle prior to study medication administration; 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 for as long as the subject remains abstinent.

Fertile men must agree to use a double barrier method of contraception (condom plus spermicide or diaphragm plus spermicide) 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 Follow-Up Visit. Female subjects found to be pregnant will be withdrawn from the study.

6.2.5.2 Action to be Taken if Pregnancy Occurs

The Investigator will collect pregnancy information on any female subject or partner of a male subject 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. Any premature termination of the pregnancy will be reported.

All pregnancies will be reported from the site and documented according to the same procedures as SAE. While a pregnancy will not be considered as an SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE.

A spontaneous abortion is always considered to be an SAE and will be reported as such. Furthermore, any SAE occurring as a result of a post-study pregnancy and which is considered reasonably related to the investigational product by the Investigator, will be reported to the Sponsor. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting. Subjects will be asked to contact the clinic in these situations.

6.2.6 Disease-Related Assessments

6.2.6.1 Urinary Sample Collections

Urine will be collected in the containers provided. Subjects will be asked to provide either two or four adequate 24-hour urine collections (ideally collected on sequential days) at the times indicated in the Time and Events Table (Appendix A). The total volume of urine and urine creatinine excretion rates will be measured from the 24-hour collections as a marker of the adequacy of the collection as detailed below in this section. **Collections judged to be inadequate may be repeated at discretion of the Investigator**.

Subjects should be instructed to avoid consuming ≥4 L/day of liquids on the day of urine collection. Subjects must also follow all of the lifestyle and dietary restrictions listed in Section 7.

At Baseline, subjects will be asked to provide four adequate 24-hour urine collections.

During the Dose Titration Phase, after the start of each dose and in order to assess the need for further dose titration, subjects will be asked to provide two adequately collected 24-hour urine specimens starting at Day 10 (±1 day) after the start of each dose level, ideally on two consecutive days. The two urine collections will be returned to the clinic on approximately Day 12. Urine volume will be measured at the clinic and samples will then be shipped frozen to the designated laboratory for measurement of UFC levels from each collection, as soon as possible upon receipt of the collections. Section 4.2.1 includes additional details of the dose titration process and determination of the

Therapeutic Dose. As part of this process, two additional adequate 24-hour urine collections will be obtained to confirm a Therapeutic Dose has been reached, prior to entry into the Maintenance Phase.

Four adequate 24-hour urine collections will be obtained just prior to the End of the Maintenance Phase visit. **These urine collections are absolutely critical to the interpretation of the study results and the subject should be made fully aware of the need for their compliance with this collection**. Prior to each monthly visit after entering the Maintenance Phase and prior to the Month 9 and 12 visit of the Extended Evaluation Phase, two adequate 24-hour collections will be obtained, ideally on two consecutive days.

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 storage of samples over 24 hours.**

The total volume of urine and urine creatinine excretion rates will be measured from the 24-hour collections as a marker of the adequacy of the collection. Total urine volume should be 400 to 4000 mL/day.

Minimum expected values for normal 24-hour creatinine excretion rates up to age 70 are provided in Table 2.

Table 2 Minimum 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.	

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 in the lower end of the ranges reported in Table 2 [Petersenn 2013].

6.2.6.2 Urinary Sample Analysis

UFC levels from the 24-hour urine collection will be assayed at a central laboratory according to the current validated methodology high pressure liquid chromatography tandem mass spectroscopy (HPLC/MS/MS). Details for handling of 24-hour UFC measurements and urine creatinine excretion rates will be provided in the SPM.

6.2.6.3 Late Night Salivary Cortisol

Late night salivary cortisol samples will be collected by each subject at the times indicated in the Time and Events Table (Appendix A). Saliva collections must be done between 11 pm and midnight and following the dietary restrictions listed in Section 7. Subjects should not sleep and subsequently awaken within two hours of collecting the saliva sample. Late night samples from two nights, will be collected at Baseline, at the beginning of Maintenance Phase (Month 1) and just prior to the End of Maintenance Phase. Late night samples from one night will be collected at all other times indicated in Time and Events Table (Appendix A). All samples will be analyzed at a central laboratory with experience in salivary cortisol measurements. All details for collection and handling of samples are provided in the SPM.

6.2.6.4 Dexamethasone Suppression Test (DST)

A DST (1 mg overnight test as described below) will need to be available at Baseline if not previously performed within the 2 months prior to start of Screening Phase, to confirm eligibility for participation in the study. In order to be fully interpretable, adherence to the timing requirement of the test will be important.

Overnight DST

- 1 mg dose of dexamethasone will be self-administered orally between 11 PM and midnight
- Blood sample to measure serum cortisol must be obtained at approximately 8 AM the next morning; the exact time to be recorded in the CRF
- Subjects will have nothing to drink or eat for at least 10 hours before the blood test.

The following medications may affect the DST results: barbiturates, corticosteroids, phenytoin, and tetracyclines.

Details of the assay are described in the SPM.

6.2.6.5 ACTH

ACTH levels will be measured in all subjects at all study visits starting with the Baseline Visit as listed in the Time and Events Table in Appendix A. Details of the assay are described in the SPM.

6.2.6.6 Pituitary Magnetic Resonance Imaging (MRI)

Pituitary MRIs will be obtained for subjects with a diagnosis of CD at Baseline, if not done within 6 months of administration of the first dose of the study drug, just prior to the End of the Maintenance Phase, and at the end of the Extension Phase. The results of MRIs obtained during the study will be evaluated by a central reader (neuroradiologist).

6.2.6.7 Oral Glucose Tolerance Test

All pre-diabetic subjects with screening fasting glucose concentrations >100 mg/dL but <126 mg/dL will have an OGTT at Baseline and at the times indicated in the Time and Events Table (Appendix A). 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 concentrations will be drawn before glucose administration and 30, 60, 90, and 120 minutes after administration. Subjects with diabetes, as defined in Appendix H will be excluded from the OGTT.

6.2.6.8 Quality of Life Measures

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 Table (Appendix A).

6.2.7 Situations Requiring Additional Safety Monitoring

Additional safety monitoring will be required for the following situations.

6.2.7.1 Dose Titration Higher than 600mg/day

If titration levels go beyond 600 mg/day, subjects are required to return once 7 days (± 3 days) after each dose level escalation visit for DL4 through DL7 for additional safety evaluations which will include the following assessments: AEs, vital signs, routine safety laboratory assessments (LFTs), ECGs, and morning serum cortisol levels (see Section 4.2.2).

6.2.7.2 QTc Prolongation

In the event QTc prolongation occurs (as defined in Section 6.2.4.1), additional safety monitoring is required, including medical observation of the subject until the QTc has returned to a value ≤500 msec or ≤60 msec change from Baseline. Additional evaluation of the subject, as described in Section 6.2.4.1, will include the potential requirement for additional ECGs, laboratory assessments and PK samples.

6.2.7.3 Adrenal Insufficiency

Subjects with suspected adrenal insufficiency should be assessed for signs and symptoms of adrenal insufficiency and cortisol levels as described in Section 6.3.3. Should adrenal insufficiency be deemed present, study drug should be temporarily discontinued for mild symptoms/signs. For moderate or severe symptoms/signs, study drug will be temporarily discontinued and rescue glucocorticoids administered as indicated. In addition, an additional PK sample should be collected as close to the time of the event as possible, ideally within several hours of dosing.

Study drug at an appropriately lower dose can be restarted once the medical situation is deemed sufficiently resolved by the Investigator. Cases of suspected adrenal insufficiency should be reported to Cmed Pharmacovigilance as AESIs (Section 13.7).

6.2.8 Pharmacokinetics

6.2.8.1 Pharmacokinetics Sample Collection

Blood samples (1 mL minimum) for the determination of plasma concentrations of COR-003 will be collected at the times indicated in the Time and Events Table (Appendix A).

The chosen dose level for PK sampling might vary from subject to subject. It is important to collect PK samples from subjects at higher dose levels. Samples will be collected from different subjects at different dose levels.

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 their medication on the day of the scheduled visit. All subjects will have a blood sample taken for PK immediately pre-dose and between 1.5 and 2.5 hours post-dose. PK samples for **at least** two different dose levels will be collected unless the Therapeutic Dose is reached at DL1. The chosen dose levels for PK sampling might vary from subject to subject**. It is important to collect PK samples from subjects at higher dose levels.** A subset of at least 10 to 15 subjects will be asked to provide a third sample around 6 to 8 hours after dosing, for at least two different dose levels.

In addition, 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 several hours of dosing (see Section 6.2.4). Additional PK samples may also be collected in association with other AESIs as close to the time of the event as possible (Section 13.2.2).

The actual PK times may vary from the nominal times; the actual dose administered, time of dose administration, and actual times of PK sample collection MUST be recorded. See SPM for further details.

6.2.8.2 Pharmacokinetics Sample Analysis

Sample analysis will be performed by Alturas Analytics (Moscow, Indiana USA) under the direction of Cortendo AB. Concentrations of COR-003 (2S,4R-ketoconazole) in plasma will be determined using current validated methodology. See SPM for further details.

6.3 Additional Considerations for Risk Management

6.3.1 Instructions for Subjects

Subjects will be instructed to carry a card at all times identifying the potential risk for adrenal insufficiency. This card will include 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 will be advised of the potential risk for adrenal insufficiency and be made aware of the signs and symptoms of this condition. At any time during the study, subjects should contact the clinical site in the event of any emerging clinical signs and symptoms of an AE. Clear instructions should be provided to the subject on how to access the medical staff at the investigational site regardless of day or time of day.

In addition, subjects will also be asked to carry an emergency kit containing hydrocortisone or another appropriate glucocorticoid, **according to local medical practice**, that can be administered immediately in case of adrenal insufficiency.

6.3.2 Considerations for Investigator

Subjects will be contacted (method by subject preference) approximately 1 week after taking the first dose and approximately 1 week after each dose adjustment to check on subject status and ensure compliance with medication administration.

Throughout the study, subjects must be monitored and managed by the Investigator for the following diseases associated with CS or its treatment, according to recommended guidelines for diagnosis and standard 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.
- Adrenal insufficiency: See the following section (Section 6.3.3) for assessment of signs and symptoms of adrenal insufficiency and Appendix K for evaluation of signs and symptoms of adrenal insufficiency.

6.3.3 Adrenal Insufficiency

All medical care providers identified by the subject, in addition to the Investigator, MUST be given sufficient written instructions about potential risks of adrenal insufficiency in subjects in this study.

It is well recognized that subjects with a good response to treatment for CS resulting in decreased, but not low, cortisol concentrations may exhibit signs and symptoms of adrenal insufficiency (non-life threatening) which may not be different than those of acute adrenal crisis, which is **a life-threatening event** warranting immediate medical intervention. Discrimination between the two may not be evident. Furthermore, subjects may have adrenal insufficiency without abnormal cortisol concentrations, but the concentrations, while within or above the normal range, are inappropriately low for the degree of physiological stress being experienced by the subject. These symptoms include: nausea, vomiting, abdominal pain, anorexia, malaise, fatigue, headache, arthralgias/myalgias, gastrointestinal discomfort, dizziness (particularly upon standing), irritability, depression, sweating, and fever. Subjects may have hypoglycemia as well. Therefore, subjects should be assessed for signs and symptoms AND cortisol levels as follows:

- Full review of symptoms.
- Lying and standing blood pressure measurements and pulse to evaluate postural changes.
- Laboratory evidence of hypoadrenalism is defined as morning serum cortisol level < 3 μg/dL (LLN or the lower limit of the assay being used for clinical testing). Even if the serum cortisol and/or the UFC are within the normal range, the possibility of adrenal insufficiency should be considered, based on postural (orthostatic) vital sign changes and clinical signs and symptoms. Please see Appendix K for a list of clinical signs and symptoms.
- Should adrenal insufficiency be deemed present, COR-003 should be temporarily discontinued for mild symptoms/signs.
- For moderate or severe symptoms/signs, COR-003 will be temporarily discontinued and rescue glucocorticoids temporarily administered.
- COR-003 at an appropriately lower dose can be restarted once the medical situation is deemed resolved. If the dose that caused adrenal insufficiency is 150 mg/day, COR-003 should be completely discontinued, and the subject withdrawn from the study.

All cases of suspected adrenal insufficiency should be reported as AESIs to Cmed Pharmacovigilance (Section 13.7).

7 LIFESTYLE AND DIETARY RESTRICTIONS

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

- Consumption of grapefruit, lime juice and Seville oranges and products (i.e. sour orange, bigarade orange, or marmalade orange) should be avoided;
- Genuine licorice should be avoided;
- Consumption of excessive alcohol should be avoided;

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 ≥4 L/day of fluids (which equals a little less than a gallon)
  - Use of medicines or products with glucocorticoids, such as hemorrhoid or steroid skin creams
- On the nights that samples are collected for **salivary cortisol test**, subjects **must refrain** from the following:
  - Within **2 hours** of the collection:
    - Brushing or flossing teeth or doing anything that could induce bleeding of the gums
    - Sleeping and subsequently awakening
  - Within **1 hour** of the collection:
    - Eating or drinking or chewing anything (including tobacco)
    - Using any creams or lotions
    - Smoking cigarettes, pipe, cigar or any other substance.

Information on subject's job related to working shift hours will be collected by the site personnel.

8 INVESTIGATIONAL PRODUCTS

8.1 Description of Investigational Product

COR-003 (2S,4R-ketoconazole, also known as levoketoconazole) will be provided as 150 mg tablets. 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 Dosage and Administration

COR-003 will be administered BID, approximately every 12 hours, according to the titration scheme described in Section 4.2. Subjects will receive an adequate number of the investigational product at each visit prepared by the study pharmacist.

8.2.1 Dosage Reduction and use of Dose Level 0

In accordance with the guidance in Section 6.3.3 if the subject develops signs and/or symptoms of adrenal insufficiency (e.g., orthostatic hypotension, nausea, vomiting, abdominal pain), based on further investigation and clinical judgment, the Investigator may opt to stop dosing of the study medication to allow resolution of these symptoms. Similarly, dosage reductions following temporary drug interruption might be used to manage possibly drug-associated toxicities, including LFT elevations (Section 5.3.2) or QTC prolongation (Section 6.2.7.2). In such cases, when the study medication is

restarted it should be reduced to the preceding dose level (as described in Section 6.2.4.2). In the event that an observation is made at DL1 necessitating dose reduction, the subject may receive a lower dose of 150 mg once daily (DL0) at the discretion of the Investigator and agreement with agreement of the Medical Monitor. Subjects may subsequently resume the Dose Titration scheme, if appropriate at the discretion of the Investigator and agreement with the Medical Monitor.

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

8.3 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 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, COR-003 is not expected to be administered at a fixed dose but will be titrated to effect in each subject. COR-003 has been used in clinical trials up to a dose of 600 mg. The highest dose of 600 mg BID COR-003 (1200 mg total daily dose) is indicated during this trial, because some CS subjects may require higher levels of cortisol suppression to achieve control in this severe disease. Any titration to a dose of COR-003 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. It is expected that titration to this highest dose will be the exception rather than the norm, based on the experience with ketoconazole and the potentially higher in vitro potency of COR-003 to inhibit key enzymes controlling adrenal cortisol synthesis. A detailed description of preclinical and prior clinical data with COR-003 and rationale for dose selection is provided in the Investigator's Brochure.

8.4 Blinding

This will be an open label study. However, a study-specific data restriction plan (DRP) has been crafted to govern the availability of efficacy data, such that the Sponsor will not be able to discern the emerging efficacy profile of the drug during study conduct, thus reducing the possibility of introduced bias.

8.5 Randomization and Treatment Assignment

This is a non-randomized study. All subjects that sign informed consent and meet eligibility criteria at Baseline will begin treatment on 150 mg BID.

9 DRUG SUPPLIES, DISPENSING, STORAGE AND ACCOUNTING

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

9.2 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 visits except for the additional safety visit required in the Titration Phase for DL4 through DL7 (where empty medication bottles and unused medication will not be collected and accountability will not be performed). Accountability to determine compliance will be performed at all other visits.

9.3 Treatment of Investigational Product Overdose

There is no known antidote to COR-003. Subjects should be medically managed according to their clinical condition, as appropriate. Refer to Section 4.2.2 for administration of doses >600 mg/day.

10 CONCOMITANT MEDICATIONS

10.1 Permitted Medications

Over the counter liquid and tablet antacids are allowed, but must be used in moderation and taken ≥2 hours after dosing with COR-003. A list will be provided.

10.2 Prohibited Medications

During the study, subjects are not allowed to take the following medications, a more complete list categorized by primary reason for prohibition is found in Appendix J. The Investigator is encouraged to contact the Medical Monitor for any questions.

- Total daily dose of acetaminophen (paracetamol) >3g (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 and rosuvastatin; potentially eligible subjects should be switched to an allowed statin several weeks prior to the Baseline Visit whenever feasible to allow equilibration of blood lipids;

- Carbamazepine, fenofibrate (assay interference), carbenoxolone;
- Genuine licorice (mineralocorticoid effects);
- Steroidogenesis inhibitors or dopamine agonists (interference with drug effect, Appendix J, Table 9 and Table 10);
- Megestrol acetate or medroxyprogesterone acetate and selected other synthetic progestins (see Appendix J, Table 11) [Schindler 2003];
- Any other drug treatments used to lower cortisol in CS that are subject to washout (Section 5.1 and Appendix J, Table 12) are prohibited throughout the study;
- Weight loss medications (either prescription or over the counter, Appendix J, Table 13);
- Drugs whose systemic exposure is potentially increased significantly by concomitant use of COR-003 (Appendix J, Table 15);
- Medications that are **strong** CYP3A4 inhibitors or CYP3A4 inducers as they may interfere with the metabolism of COR-003. As examples, rifampicin, rifabutin, isoniazid, nevirapine and phenytoin may significantly reduce COR-003 concentrations via CYP3A4 induction, and ritonavir may increase COR-003 concentrations via CYP3A4 inhibition, and are therefore prohibited (Appendix J, Table 16);
- Medications resulting in QTc prolongation as a direct effect or as a result of interaction with COR-003, examples include: cisapride, dofetilide, pimozide, quinidine. (Appendix J, Table 17). 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 9);
- 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 20). 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 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 increases 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 that case, careful monitoring, with possible adjustments in doses, is recommended (see Appendix J, Table 18).

11 SUBJECT COMPLETION AND WITHDRAWAL

11.1 Subject Completion

Subjects who complete the End of Maintenance Phase Visit of the study, regardless of their response status, will be considered to have completed the study and are eligible for inclusion into the Extended Evaluation Phase.

Subjects who complete the Extended Evaluation Phase (M12 Visit) and are not progressing into an expanded access program should return approximately 2 weeks after completion of treatment with COR-003 for the Follow-Up Visit (see Appendix A).

11.2 Subject Withdrawal Criteria and Procedures

Reasons for premature study withdrawal (i.e. do not return for all study visits), include, but are not limited, to the following (see also Section 5.3):

- Safety reasons, either at the discretion of the Investigator or at the subject's request
- Protocol violations at the discretion of the Sponsor
- Permanent study medication discontinuation
- 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).

All study withdrawals and their causes must be carefully documented 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 all safety and PK assessments as outlined for the Follow-Up Visit in Appendix A (approximately 2 weeks following end of treatment with COR-003). If a subject is withdrawn before completing the Maintenance or Extended Evaluation Phases of the study, the reason for termination will be recorded. All data gathered on the subject prior to termination will be made available to the Sponsor.

12 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

12.1 Population for Analysis

Intent-to-Treat (ITT) Population: The ITT population will include all subjects who receive at least one dose of COR-003. This population will be used for the evaluation of efficacy and all safety analyses.

Maintenance (M) Population: The M population will consist of all subjects who enter the Maintenance Phase of the study. This population will be used for the supportive evaluation of all the primary and secondary efficacy endpoints.

Per Protocol (PP) Population: The PP population will consist of all subjects who enter the Maintenance Phase of the study and have no major protocol deviations that may affect efficacy. This population will be as supportive analysis for the analysis of the primary endpoint.

12.2 Hypothesis

The primary endpoint for this study will be the proportion of responders to COR-003 following 6 months of dosing in the Maintenance Phase without a dose increase during that phase. Additionally, subjects who previously received radiation therapy and who exhibit no rebound increase in mean UFC following withdrawal of COR-003 immediately after the end of the Maintenance Phase will be considered non-responders.

The proportion of responders in the ITT population will be estimated along with corresponding two-sided 95% confidence interval (CI). The null hypothesis to be tested is if the proportion of responders at the end of the Maintenance Phase visit is at most 20% versus the alternative hypothesis that the proportion of responders at the end of the Maintenance Phase visit is greater than 20%; COR-003 will be considered effective if the null hypothesis is rejected. The hypothesis test is to have 90% power and two-sided 5% Type I error.

12.3 Sample Size Determination

A sufficient number of subjects (estimated at approximately 90) will be enrolled into the Dose Titration Phase of the study to ensure that at least 70 subjects complete the 6-month Maintenance Phase. The 90 subjects to be enrolled in the Dose Titration Phase will constitute the primary analysis population (i.e. the ITT population). Table 3 illustrates the power to exclude the null hypothesis of at most a 20% responder rate, given an alternative response of 35% for a two-sided 5% Type I error for the ITT population. Results will be evaluated using a two-sided 95% lower confidence bound for the response rate at the end of the Maintenance Phase visit.

Table 3 One Sample χ^2 Test: Null Hypotheses vs. Alternative Hypothesis, One Scenario

Test significance level, α	0.050
1 or 2 sided test?	2
Null Hypothesis Responses %, p_0	20%
Alternative Hypothesis Response %, p_A	35%
Power (%)	90
N (ITT)	90

As an example, if the observed response rate at the end of the Maintenance Phase visit is 40% with 90 subjects, then the two-sided 95% CI is (30.0%, 50.9%) which would support efficacy.

In addition, the sample size of 90 subjects will be adequate to test hypotheses associated with the change from Baseline in CS comorbidity biomarkers expressed as continuous

endpoints (secondary efficacy endpoints). Table 4 displays the differences that can be detected for the secondary efficacy endpoints of CS comorbidities with 90% power for a two-sided 1% Type I error for 90 subjects (the 1% Type I error accounts for testing significance for these multiple secondary efficacy endpoints). Results will be evaluated using two-sided 99% lower confidence bounds for the changes from Baseline at the End of the Maintenance Phase visit.

Table 4 Paired t-test: No (0) Mean Differences Null Hypotheses vs. Anticipated Mean Differences Alternative Hypothesis

	Glucose [mmol/l][1]	HbA1c [%]	SBP [mm Hg]	DBP [mm Hg]	Total Cholesterol [mmol/L]	LDL [mg/dL]	Weight [kg][2]
Test significance level, α	0.010	0.010	0.010	0.010	0.010	0.010	0.010
1 or 2 sided test?	2	2	2	2	2	2	2
Mean difference, m_d	0.670	0.311	8.743	6.174	0.497	0.535	2.445
SD difference, s_d	1.600[1]	0.750[1]	21.1[2]	14.9[2]	1.2[3]	1.29[2]	5.9[2]
Effect size, $d = \|m_d\| / s_d$	0.419	0.414	0.414	0.414	0.414	0.414	0.414
Power (%)	90	90	90	90	90	90	90
N	90	90	90	90	90	90	90

1. Fleseriu 2012
2. Colao 2012
3. FDA Medical Review document for pasireotide

12.4 General Considerations for Data Analysis

The SAS System, Version 9.1.3 (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.

12.4.1 Premature Withdrawal and Missing Data

Subjects withdrawn prior to the end of the Maintenance Phase will be considered as prematurely withdrawn. All available data for subjects who prematurely withdraw from the study will be included in all analyses. At any visits for which four 24-hour urine samples are planned to be collected, at least two UFC collections must be adequate by volume and creatinine criteria to be able to derive the mean UFC and thus be considered as non-missing. Study withdrawals, reasons for withdrawal, and missing UFC collections will be summarized.

Analyses of data for specific visits will be performed using two different approaches to account for missing data during the Maintenance Phase:

1. At-Visit analysis: Missing values at post-Baseline assessments will not be replaced and will be regarded as missing in longitudinal analyses. The longitudinal models account for missing data.
2. Imputation analysis: Subjects withdrawing will be counted as failures for the primary efficacy analyses.

At-visit analyses will be performed using the longitudinal models as the primary approach with the imputation approach as supportive. Details will be provided in the SAP.

12.5 Final Analyses

12.5.1 Safety Analyses

The final analysis of safety is considered to be coincident with the last subject visit following completion of the Extended Evaluation Phase (i.e. following at least 12 months' treatment at the Therapeutic Dose). Interim analyses of safety are planned to coincide with timing for the primary analysis of efficacy (i.e. after the final subject has completed Maintenance Phase) and for any unplanned interim efficacy analyses, in order to assess benefits and risks of treatment simultaneously. In addition, planned and unplanned safety analyses will be performed and reported on a limited basis in order to satisfy requirements of study oversight, for example to Institutional Review Boards and Competent Authorities. These limited analyses (e.g. common adverse reactions summary) will not be accompanied by assessments of potential benefits.

The DSMB will review all SAEs and AESIs on a rolling basis and assess benefits and risk of therapy systematically at approximately 6-month intervals.

12.5.1.1 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.

Study drug compliance between visits and cumulative study drug compliance will be calculated by dividing the number of study drug tablets used (total number dispensed minus total number returned/lost/wasted) by the total number of study drug tablets that should have been taken and multiplying the result by 100.

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

12.5.1.2 Adverse Events (AEs)

AEs will be coded using MedDRA and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 [NCI CTCAE, 2009].

TEAEs will be of primary interest. The proportion of subjects reporting at least one TEAE, at least one drug-related TEAE, at least one serious TEAE, at least one TEAE leading to discontinuation of study drug, and at least one TEAE leading to withdrawal from the study will be computed. The number and the percentage of subjects reporting each TEAE will be summarized for all TEAEs, and separately for drug-related TEAEs, all serious TEAEs, all TEAEs leading to discontinuation of study drug, and all TEAEs leading to withdrawal from the study.

The most common TEAEs are defined as those occurring in at least 5% of the ITT population. The number and the percentage of subjects reporting the most common TEAEs will be summarized. Two-sided 95% CIs will be reported for such TEAEs.

12.5.1.3 Clinical Laboratory Evaluations

A laboratory value that is within the normal range will be considered normal. A laboratory value that is outside the testing laboratory's normal range will be considered an abnormal laboratory value. The number and percentage of subjects with abnormal laboratory values will be summarized for each scheduled visit. Shift tables will be constructed.

Differences in laboratory values between Baseline and each scheduled laboratory assessment will be calculated for each laboratory test and summarized descriptively. The laboratory test values obtained at Baseline closest to the start of treatment will be used as the Baseline value.

Further details of the categorical analysis of the laboratory evaluation and on the LFT evaluations will be defined in detail in the SAP.

12.5.1.4 Vital Signs

Heart rate and three measurements of SBP and DBP will be taken at each visit. The mean of these measurements will be used as the value for each visit. Baseline will be defined as the mean of the values from the measurement at Baseline just prior to the start of treatment. Change from Baseline for each measurement will be summarized. 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)	< 44 bpm	Low (L)
	44-100 bpm	Normal
	101-120 bpm	High (H)
	>120 bpm	Very High (VH)
Systolic Blood Pressure (SBP)	< 90 mm Hg	Low (L)
	90-139 mm Hg	Normal
	140-169 mm Hg	High (H)
	≥170 mm Hg	Very High (VH)
Diastolic Blood Pressure (DBP)	< 50 mm Hg	Low (L)
	50-89 mm Hg	Normal
	90-109 mm Hg	High (H)
	≥ 110 mm Hg	Very High (VH)

The number and percentage of subjects with blood pressure and HR outside the pre-defined range of clinical concern at any post-Baseline assessment will be summarized.

Shift tables for normal vs abnormal vital signs from Baseline to each scheduled assessment will be constructed.

12.5.1.5 Electrocardiograms (ECGs)

Summary ECGs, based on the measurement of an ECG over 5 minutes as described in Section 6.2.4 will be used for each evaluation. Quantitative ECG measurements (PR interval, QRS duration, HR, QT interval, QTcB interval, and QTcF interval) and changes from Baseline will be summarized descriptively. ECGs results will be available to the Investigator shortly after being obtained and all ECGs will be reviewed by a central consulting cardiologist. The data from the central consulting cardiologist will be used in the evaluation of the drug effect. While on study treatment, a QTc > 500 msec or > 60 msec above Baseline will be of special interest (See Section 13.2.2).

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

Table 6. QTc Interval Values of Clinical Importance

QTc Interval	Criteria (msec)	Flag
Change from Baseline	<30	Low (L)
	30-60	Mid (M)
	>60	High (H)
Actual Value	>450-480	Low (L)
	>480-500	Mid (M)
	>500	High (H)

Continuous ECG outcomes will be assessed using a paired t-tests while normal-abnormal shift tables will be assessed using a McNemar's paired comparison tests.

12.5.1.6 Other Safety Measures

Results from the DST during the Screening Phase will be listed by subject. ACTH, IGF-1 and testosterone levels will be listed and summarized descriptively by time point. Results from pituitary MRI (tumor size) will be listed by subject and time point and descriptively summarized.

12.5.2 Efficacy Analyses

All efficacy analyses will be performed on the ITT and M populations using longitudinal models. For the primary endpoint, imputation will be applied for subjects that were prematurely withdrawn from the study as supportive analysis. In addition, the primary endpoint will also be analyzed using the PP population as supportive analysis.

Withdrawn subjects prior to the End of the Maintenance Phase Visit assessment, as well as those requiring a dose increase during the Maintenance Phase, will be considered non-responders as long as the dose increase was sustained. Additionally, subjects who previously received radiation therapy and who exhibit no rebound increase in mean UFC following withdrawal of COR-003 immediately after the end of the Maintenance Phase will be considered non-responders.

12.5.2.1 Primary Efficacy Analysis

Clinical Response Rate

UFC data will be averaged for the End of Maintenance Phase Visit and then analyzed for response. The treatment estimate of the clinical response rate at the end of the Maintenance Phase and its associated two-sided 95% CI will be obtained from a repeated measures GEE model with a logit link using SAS PROC GLIMMMIX with LSMEANS statement. The primary analysis will be the ITT population and analysis will be repeated in the M population and PP population. The longitudinal model will include visit, the concurrent CS medical conditions (diabetes, hypertension) as Baseline covariates as well as age (rounded median split), sex, disease duration, prior CS therapy, and prior radiation therapy, and subject will be included as a random effect.

Dose level information for the M population and PP population will be summarized.

If the lower bound of the 95% CI for the LSMEAN proportion of responders in the ITT population is ≥20% in the ITT population, then COR-003 will be considered effective.

Although the End of Maintenance Phase marks the final analysis of primary efficacy, the clinical response rate will also be analyzed after each month of treatment in the Maintenance Phase and (secondary endpoint) and after 9 and 12 months in the extension phase (exploratory endpoint).

12.5.2.2 Secondary Efficacy

UFC Analysis

Clinical Response Rates

UFC data will be averaged at each nominal visit and then analyzed for response in the same manner as for primary endpoint using the longitudinal models described in Section 12.5.2.1. The proportion of UFC responders to COR-003 (defined similarly to the primary endpoint) along with associated 95% CIs will also be individually estimated at Months 1, 2, 3, 4, and 5 of the Maintenance Phase. The longitudinal model estimates and the Nominal Visit estimates will both be presented.

Complete and Partial Response Rates

The proportion of subjects with complete and partial responses (≥ 50% reduction in mean UFC from Baseline at Months 1, 2, 3, 4, 5, and 6 of the Maintenance Phase) will be calculated and reported alongside with its associated 95% CIs and will be estimated from a repeated measurement model with the same covariate as for the primary endpoint analysis.

Change in UFC

Mean UFC will be calculated from adequate 24-hour urine collections. At Baseline and End of Maintenance Phase where four samples are to be collected, the mean UFC will only be calculated if there are at least two adequate samples. The mean UFC from the collections at each visit will be used in the analysis of UFC. UFC will be summarized by time point using descriptive statistics. In addition, change from Baseline and percent change from Baseline will be calculated for each post-Baseline assessment. Mean and individual plots of each endpoint over time will be presented for the Maintenance Phase. Paired t-tests will also be presented for the change from Baseline to each nominal visit.

In addition, a shift table will be created to summarize the shift from Baseline to each post-Baseline time point using the following UFC normality categories: less than LLN, normal range, greater than ULN and less than 2X ULN, 2X to 5X ULN, 5X ULN to 10X ULN, greater than 10X ULN. Shift analyses will be conducted using a generalized McNemar paired comparison test to account for the multiple categories.

Salivary and Serum Cortisol Levels

Mean salivary and serum cortisol levels will be calculated after 1, 2, 3, 4, 5, and 6 months of dosing in the Maintenance Phase. Change from Baseline and percent change from Baseline and at-visit values will also be listed and summarized descriptively by visit. Values at each post-Baseline Visit will be compared with Baseline using a paired t-test.

CS Comorbidity Biomarkers

The changes from Baseline and percentage change from Baseline in individual biochemical markers of CS comorbidities (fasting glucose, HbA1c, SBP, DBP, total cholesterol, LDL and HDL cholesterol, and body weight) will be summarized at Months

1, 2, 3, 4, 5, and 6 of the Maintenance Phase. In addition, shifts from Baseline (with regards to laboratory normal range) in individual biochemical markers of CS comorbidities will be analyzed using a t-test paired comparison test at each scheduled visit.

Calculations for the CS comorbidity biomarkers will be performed using SAS PROC MIXED to account for all post-Dose Titration Phase outcomes per subject with changes from Baseline and two-sided 99% lower confidence bounds calculated using LSMEANS. To account for endpoint multiplicity, conservative 99% CIs will be computed instead of 95% CIs. The longitudinal model will include visit, the concurrent CS medical conditions (diabetes, hypertension) as Baseline covariates as well as age (rounded median split), sex, disease duration, prior CS therapy, and prior radiation therapy, and subject as a random effect.

Clinical Signs and Symptoms

Each individual clinical sign and symptom, defined in Appendix M, will be summarized at each time point for assessment by number and percent of subjects.

Each sign and symptom present at Baseline will be graded on a 0 to 3 severity scale (0=absent, 1=mild, 2=moderate, 3=severe). For each subject, the severities will be added. A paired t-test will be used to test if there is a significant reduction in severity at each visit.

In addition, shift tables in individual clinical signs and symptoms at each post-Dose Titration Phase visit will be created to demonstrate any improvement gained during the course of treatment and analyzed using a McNemar paired comparison test.

Cushing's Syndrome Quality of Life Questionnaire

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

Beck's Depression Questionnaire

Changes from Baseline for the Beck's Depression questionnaire (Appendix N) will be summarized by time point using descriptive statistics and analyzed using a paired t-test. Only subjects recruited under the protocol amendment or subsequent amendment will be included in the summary table. All data will be listed.

Glucose Tolerance Test

For pre-diabetic subjects as determined by the Investigator as Baseline, the number and percent of subjects after 3 and 6 months of dosing in the Maintenance Phase will be summarized for each of the following categories.

- Normal: 2-hour glucose level is <140 mg/dL
- Impaired glucose tolerance (pre-diabetic): glucose level ≥140 mg/dL and ≤200 mg/dL
- Provisional diagnosis of diabetes (diabetic): glucose level ≥200 mg/mL

Glucose 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.

Spot Albumin/Creatinine Ratio

For subjects who have abnormal albumin/creatinine ratio at Baseline, albumin/creatinine ratio and its change from Baseline after 3 and 6 months of dosing in the Maintenance Phase will be summarized. At-visit values will be compared with Baseline using a paired t-test.

CRP

CRP value and its change from Baseline after 1, 2, 3, 4, 5 and 6 months of dosing in the Maintenance Phase will be summarized.

12.5.2.3 Exploratory Efficacy

The analyses described above in Section 12.5.2.2 for clinical response rate, complete and partial response rate, changes in UFC, serum and late night salivary cortisol, QoL (Cushing's QoL questionnaire and Beck's Depression Index), and change in CS comorbidities, OGTT, albumin/creatinine and CRP will be repeated for the Extended Evaluation period using the same approach as for the Maintenance Period.

Clinical Benefit

The proportion of subjects achieving clinical benefit at Months 1, 2, 3, 4, 5, and 6 during the Maintenance Phase and Months 9 and 12 in the Extended Evaluation Phase will be displayed graphically over time with clinical benefit defined as:

1. Clinical response as indicated by UFC ≤ ULN, and
2. No increase in COR-003 dose during Maintenance Phase, and
3. A clinically meaningful improvement in any one Baseline CS comorbidity (diabetes, hypertension, hypercholesterolemia, weight) as will be defined in the SAP and
4. No study drug related TEAE classified as severe or worse.

Medication Changes

Changes to concomitant medications (in particular for blood pressure, diabetes and cholesterol management) will be listed by subject. In addition, the number and percent of subjects with medication changes during the course of the study will be summarized. The proportions with dose increases and decreases including new and discontinued medications will be displayed.

Clinical Signs of Hypercortisolism (Photographs)

At Baseline, End of Maintenance Phase Visit, and End of Extended Evaluation Phase Visit, the adjudication committee, composed of three clinician-investigator experts in CS will assess the subjects for changes in visible signs of hypercortisolism (e.g. moon face, plethora, supraclavicular and dorsal fat pads, striae, hirsutism, bruising and overall body

habitus, if available) by scoring longitudinal photographs. The scoring will be based on overall subjective impression of changes from Baseline as follows: obvious visible worsening, subtle visible worsening, no visible changes, subtle visible improvements, obvious visible improvements. Other methods of scoring photos may be included in the SAP.

Relationship Between QTc Interval and COR-003

The number and percentage of subjects with abnormal QTc, QTcB and QTcF results (abnormal categories are defined as > 450 msec, > 480 msec, > 500 msec, > 30 msec increase from Baseline and > 60 msec increase from Baseline) will be summarized for each dose level after 1, 2, 3, 4, 5 and 6 month of treatment in the Maintenance Phase and after 9 and 12 months in the Extended Evaluation Phase. Subjects will be summarized under their therapeutic dose or the maximum dose reached during the Dose Titration Phase if the subject discontinued prior to entering the Maintenance Phase.

12.5.3 Pharmacokinetics Analysis

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.

PK data will be evaluated using a population modeling-based approach 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.

12.5.4 Pharmacodynamics Analysis

The PD model parameters including UFC Imax, COR-003 dose producing UFC IC50, and associated estimates of between subject variability will be reported. Individual maximal UFC reductions achieved 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.

PD data (UFC) will be evaluated using a population modeling-based approach 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.

12.5.5 Subgroup Analyses

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

12.5.5.1 Prior Therapy for Cushing's Syndrome

Subgroup displays for the primary endpoint and the CS comorbidities endpoints will be generated for subjects that enter the study as medical treatment-naïve vs. medical treatment-experienced and 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.

12.5.5.2 Prior Radiation Therapy

Subset displays for the primary endpoint and the CS comorbidities endpoint will be generated, excluding subjects who previously received radiation therapy. The total number of previously irradiated subjects will not exceed 10.

Note: A drug holiday after the last Maintenance Phase visit will be used to determine if UFC normalization during the Maintenance Phase can be attributed to COR-003 or to prior radiation therapy (i.e. a loss of normalization during temporary drug interruption will implicate COR-003 as primarily responsible for UFC normalization).

12.5.5.3 Hypertensive Subjects

Subgroup displays for the primary endpoint and the 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 >130 mmHg or DBP $\geq$90 mmHg regardless of antihypertensive medication status versus those with lower BP recordings.

12.5.5.4 Pre-diabetic/Diabetic Subjects

Subgroup displays for the primary endpoint and the CS comorbidities secondary efficacy endpoint will be performed for subjects who enter the study as pre-diabetic (Baseline fasting serum glucose >100 mg/dL but <126 mg/dL without concomitant use of antihyperglycemic medication) versus those with normal fasting glucose or diabetic (Baseline fasting serum glucose $\geq$126 mg/dL or lower fasting glucose while being prescribed antihyperglycemic medications) versus those without diabetes. Subgroups based on findings from stimulated glucose during the Baseline OGTT will also be generated.

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 or not related to the study drug or study conduct.

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

13.2 Definition of a SAE

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

(a) results in death;

(b) is life-threatening;

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

(c) requires hospitalization or prolongation of existing hospitalization;

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

(d) results in disability/incapacity;

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

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

(f) Medical or scientific 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 in order 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 >500 msec (or >60 msec above Baseline), with an ECG evaluation on repeat determination continuing to demonstrate QTc prolongation in the absence of plausible alternative explanations.

- **Potential hepatic events:** Signs of hepatic dysfunction, such as:

  - ALT or AST >8X ULN
  - ALT or AST rises to >5X ULN in <4 weeks or persists for >2 weeks
  - ALT or AST >3X ULN **and** TBN >2X ULN or INR >1.5 not explained by any other cause such as viral hepatitis, and without evidence of cholestasis
  - ALT or AST >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 >3X ULN and/or AP >2X ULN, and/or TBN >2X ULN in the absence of evidence for obstruction or Gilbert syndrome. An ultrasound evaluation of the gallbladder and bile duct should be conducted to exclude cholestasis as the cause for elevated AP and/or TBN.

- **Adrenal insufficiency:** A suspicion or diagnosis of adrenal insufficiency, based on the considerations laid out in Section 6.3.3.

13.3 Time Period, Frequency, and Method of Detecting AEs and SAEs

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

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. In order 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 according to 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

SAEs will be classified as "**not related**" or "**related**" (including unknown).

For AEs, the relationship to study treatment is to be assessed according to the following definitions:

Definitely 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).

Unlikely: There is no reasonable association between the study treatment and the suspected event and the event could have been produced by the subject's clinical state or other modes of therapy administered to the subject.

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.

Probable: 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 "SAE" CRF within 24 hours.

13.7 Prompt Reporting of SAEs to Sponsor

Any SAE, occurring in a subject who has signed the informed consent or if the Investigator becomes aware of any SAE post-treatment during the follow-up period, 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, telephone and fax numbers listed below should be used to notify the Sponsor.

Cortendo Reportable Events Hotline

Email: sae@cmedresearch.com

24 Hour Phone: 0044 (0)1403 758462

US Toll-Free Phone: 1 866 966 8429

Fax: 0044 (0)1403 330459

US Toll-Free Fax: 1 866 966 2970

An SAE Report form must be completed and forwarded via email or facsimile to Cortendo's designated safety group using the email address or fax number 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 Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) are notified of the SAE.

14 REFERENCES

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

Bochicchio D, Losa M, Buchfelder M. Factors influencing the immediate and late outcome of Cushing's disease treated by transsphenoidal surgery: a retrospective study by the European Cushing's Disease Survey Group. J Clin Endocrinol Metab. 1995 Nov;80(11):3114-20.

Brodovicz, KG, McNaughtan K, Uemura N, Meininger G, Girman CJ, Yale SH. Reliability and Feasibility of Methods to Quantitatively Assess Peripheral Edema. Clin Med Res 2009;7(1/2):21-31

Castinetti F, Guignat L, Giraud P, et al. Ketoconazole in Cushing's disease: is it worth a try? J Clin Endocrinol Metab. 2014;99:1623-1630.

Colao A, Petersenn S, Newell-Price J, Findling J, Gu F, Maldonado M, Schoenherr U, Mills D, Salgado R, and Biller B for the Pasireotide B2305 Study Group. A 12-Month Phase 3 Study of Pasireotide in Cushing's Disease. N Engl J Med 2012; 366, 914-924.

Cortendo Report Number 2002-02-21, Cortendo Exp IIId and Report Number 2002-02-21, Cortendo Exp IVa. 2002.

Cortendo Report Number DIO-501, A phase 1/2a, randomized, placebo-controlled, double-blind, parallel-group, study of safety, tolerability, pharmacokinetics and activity of 14 days of oral dosing with the 2s,4r enantiomer of ketoconazole (dio-902) in subjects with type 2 diabetes mellitus. 10 April 2007

Dalton G. Transsphenoidal hypophysectomy for pituitary tumours. Proc R Soc Med. 1974 Sep;67(9):885-9.

Daneshmend TK, Warnock DW. Clinical Pharmacokinetics of Ketoconazole. Clinical Pharmacokinetics. 1988;14:13-34.

Daniel E, Newell-Price JD. Therapy of endocrine disease: steroidogenesis enzyme inhibitors in Cushing's syndrome. European Journal of Endocrinology, European Federation of Endocrine Societies. 2015;172(6):R263-280.

De Martin M, Pecori Giraldi F, Cavagnini F. Cushing's disease. Pituitary. 2006;9(4):279-87.

Doshi A, Zaheer A, Stiller MJ. A comparison of current acne grading systems and proposal of a novel system. Int J Derm. 1997;36:416-418

Engelhardt D, Weber MM, Miksch T, Abedinpour F, Jaspers C. The influence of ketoconazole on human adrenal steroidogenesis: incubation studies with tissue slices. Clinical Endocrinology. 1991; Aug;35(2):163-8.

Fleseriu M, Biller BMK, Findling J, Molitch M, Schteingart D, Gross C on behalf of the SEISMIC Study Investigators. Mifepristone, a Glucocorticoid Receptor Antagonist, Produces Clinical and Metabolic Benefits in Patients with Cushing's Syndrome. J Clin Endocrinol Metab 2012; 97: 2039-2049.

Gerber JD, Dilmaghania S, Gal J. Stereoselective pharmacokinetics (PK) of oral ketoconazole (K) in healthy subjects. Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) September 2003; poster #A-1569.

Giraldi FP, Toja PM, Michailidis G, Metinidou A, De Martin M, Scacchi M, Stramba-Badiale M, Cavagnini F. High Prevalence of Prolonged QT Interval Duration in Male Patients with Cushing's Disease. Exp Clin Endocrinol Diabetes 2011; 119:221-224.

Hatch R, Rosenfield RL, Kim MH, Tredway D. Hirsutism: implications, etiology, and management. Am J Obstet Gynecol. 1981;140:815-830.

Ketoconazole HRA Assessment Report. September 25, 2014. Committee for Medicinal Products for Human Use. EMA/CHMP/534845/2014.

Kreutzer J, Jeske I, Hofmann B, Blumcke I, Fahlbusch R, Buchfelder M, et al. No effect of the PPAR-gamma agonist rosiglitazone on ACTH or cortisol secretion in Nelson's syndrome and Cushing's disease in vitro and in vivo. Clin Neuropathol. 2009 Nov-Dec;28(6):430-9.

Kucers A, Hoy JF, Lindsay Grayson M, Crowe SM. The Use of Antibiotics: A Clinical Review of Antibacterial, antifungal and antiviral drugs. In: Butterworth, Hindman, editors. 5 ed: Oxford University Press; 1997. p. 1358-84.

Lake-Bakaar G, Scheuer PJ, Sherlock S. Hepatic reactions associated with ketoconazole in the United Kingdom. Br Med J. 1987;294:419-422.

Lewis JH, Zimmerman HJ, Benson GD, Ishak KG. Hepatic injury associated with ketoconazole therapy. Analysis of 33 cases. Gastroenterology. 1984;86:503-513.

Lindholm J, Juul S, Jorgensen JO, Astrup J, Bjerre P, Feldt-Rasmussen U, et al. Incidence and late prognosis of cushing's syndrome: a population-based study. J Clin Endocrinol Metab. 2001 Jan;86(1):117-23.

Mancini T, Kola B, Mantero F, Boscaro M, Arnaldi G. High cardiovascular risk in patients with Cushing's syndrome according to 1999 WHO/ISH guidelines. Clinical endocrinology. 2004 Dec;61(6):768-77.

National Cancer Institute. Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0. June 14, 2014 http://ctep.cancer.gov/protocolDevelopment/

Nieman LK, Biller BMK, Findling JW, et al. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. J. Clin Endocrinol & Met. 2008;93(5):1526-1540.

Nieman LK. Medical therapy of Cushing's disease. Pituitary. 2002;5(2):77-82.

Nizoral® Product Insert. Janssen Pharmaceuticals. July 2013.

Petersenn S, Newell-Price J, Finding JW, Gus F, Maldonado M, Sen K, Salgado LR, Colao A, and Biller BMK on behalf of the Pasireotide B2305 Study Group. High variability in Baseline urinary free cortisol values in patients with Cushing's disease. Clin Endocrinol. 2013; 0: 1-9.

Pivonello R, Faggiano A, Lombardi G, Colao A. The metabolic syndrome and cardiovascular risk in Cushing's syndrome. Endocrinol Metab Clin North Am. 2005 Jun;34(2):327-39, viii.

Pozza C, Graziadio C, Giannetta E, Lenzi A, Isiori A. Management strategies for aggressive Cushing's syndrome: from macroadenomas to ectopics. J Oncol. 2012;(2012),Article ID 685213, 9 pages.

Rotstein DM, Kertesz DJ, Walker KA, Swinney DC. Stereoisomers of ketoconazole: preparation and biological activity. J Med Chem. 1992 Jul 24;35(15):2818-25.

Schindler AE, Campagnoli C, Druckmann R, Humber J, Pasqualini JR, Schweppe KW, Thijssen JHH. Classification and pharmacology of progestins. Maturitas. 2003; 46S1: S7-S16.

Schwartz SL, Rendell M, Ahmann AJ, Thomas A, Arauz-Pacheco CJ, Welles BR. Safety profile and metabolic effects of 14 days of treatment with DIO-902: results of a phase IIa multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in patients with type 2 diabetes mellitus. Clin Ther. 2008 Jun;30(6):1081-8.

Sharma ST, Nieman LK. Cushing's syndrome: all variants, detection, and treatment. Endocrinol Metab Clin North Am. 2011 Jun;40(2):379-91, viii-ix.

Sonino N. The use of ketoconazole as an inhibitor of steroid production. N Engl J Med. 1987;317:812-8.

Steen RE, Kapelrud H, Haug E, Frey H. In vivo and in vitro inhibition by ketoconazole of ACTH secretion from a human thymic carcinoid tumour. Acta endocrinologica. 1991 Sep;125(3):331-4.

Steffensen C, Bak AM, Rubeck KZ, Jorgensen JO. Epidemiology of Cushing's syndrome. Neuroendocrinology, 2010;92: Suppl 1: 1-5

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)—Complete Report. August 2004.

Webb SM, Badia X, Barahona MJ, et al. Evaluation of health-related quality of life in patients with Cushing's syndrome with a new questionnaire. Eur J Endocrinol 2008;158;623-30.

Whitehouse LW, Menzies A, Mueller R, Pontefract R. Ketoconazole-induced hepatic phosphplipidosis in the mouse and its association with de-N-acetyl ketoconazole. Toxicology. 1994;94:81-95.

APPENDIX A TIME AND EVENTS SCHEDULE

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

Time and Events Schedule															
Assessments	**Screening Phase**		**Dose Titration Phase[1]**			**Maintenance Phase[2]**							**Extended Evaluation Phase[3]**		**FU Visit[4]**
	Scrn[5]	**Baseline[6]**	**DL1 (DL0)**	**DL2 DL3**	**DL4 DL5 DL6 DL7**	**M 1**	**M 2**	**M 3**	**M 4**	**M 5**	**M 6**	**End of MP**	**M 9**	**M 12**	
Informed Consent	X														
Eligibility (Check Inclusion/Exclusion Criteria)	X	X													
Medical History [7] and demography	X	X													
Prior/concomitant medication [8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Administer drug/drug accountability			X	X	X	X	X	X	X	X	X	X	X	X	
Physical exam & assessment of appearance	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of Signs & Symptoms form[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[1] The approximate interval between dose adjustments will be 18 days (±4 days) including reporting time for UFC levels and safety laboratory assessments. If additional UFC collections are required, the approximate interval between either dose adjustments or to transition to maintenance should be 30 days (±7 days) to allow for additional testing and reporting time. DL0 is a lower dose of **150 mg once daily** that may be used if the subject develops signs and/or symptoms of adrenal insufficiency at DL1 and is to be restarted on a reduced the dose after their resolution (see Section 6.3.3 and 6.2.4.2).
[2] Maintenance visits should occur every 30 days (±7 days).
[3] Extended Evaluation visits should occur every 90 days (±14 days).
[4] Subjects who complete the Extended Evaluation Phase (M12 Visit) and are not progressing into an expanded access program should return approximately 2 weeks after completion of treatment with COR-003 for the Follow-up Visit (and no later than 30 days). NOTE: The Follow-Up Visit is not required for subjects continuing into expanded access treatment.
[5] Screening procedure to be performed following ICF and PRIOR to washout (if necessary)
[6] Baseline procedures should be performed within 14 days (± 7 days) of DL1 visit.
[7] Medical history to include previous documentation of diagnosis of Cushing's syndrome, and data on all previous LFTs, as medical records permit. Medical histories should be updated at Baseline.
[8] Blood pressure, diabetes, cholesterol medications will be specifically reviewed.
[9] Assessment of Clinical Signs & Symptoms form (Appendix M) to be completed along with the physical exam once at each dose level during the Dose Titration Phase and at each visit during the Maintenance and Extended Evaluation Phases

Time and Events Schedule															
Assessments	**Screening Phase**		**Dose Titration Phase[1]**			**Maintenance Phase[2]**							**Extended Evaluation Phase[3]**		**FU Visit[4]**
	Scrn[5]	**Baseline[6]**	**DL1 (DL0)**	**DL2 DL3**	**DL4 DL5 DL6 DL7**	**M 1**	**M 2**	**M 3**	**M 4**	**M 5**	**M 6**	**End of MP**	**M 9**	**M 12**	
Vital signs (BP and HR in triplicate and temperature)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight/height/body habitus	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Abdominal Girth (in triplicate)		X				X			X			X	X	X	X
HIV / Hepatitis B and C blood test	X														
Photographs (consenting subjects only)		X							X			X		X	X
ECG – Local ECG machine	X														
ECG – Spaulding[10]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact subject 1 week after a new dose			X	X											
Additional safety evaluation [11] (e.g., day 7 [±3 days])					X										
Late night salivary cortisol (1 night)							X	X	X	X	X		X	X	X
Late night salivary cortisol (2 nights)		X				X						X			
TSH / free T4 [12]	X				X	X		X		X		X	X	X	X
Pituitary MRI (CD only)		X [13]										X		X	
FSH (women only)	X														
Urine βHCG, females	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety clinical laboratory	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
INR/PT/PTT		X				X	X	X	X	X	X	X	X	X	X
HbA1c	X	X				X			X			X	X	X	X

[10] Spaulding ECGs will be obtained over a maximum of 5 minutes at Baseline and within approximately 1 – 2 h after drug administration at each dose level during Dose Titration Phase and at each visit during the Maintenance and Extended Evaluation Phases

[11] Additional safety assessments at higher dose levels to include: AEs, vital signs, routine safety laboratory assessments (including LFTs), ECGs, and serum cortisol levels.

[12] TSH/free T4 to be measured at DL4 Visit during the Dose Titration Phase. If subjects reach their maximum dose before the DL4 visit during the Dose Titration Phase, they will have TSH/free T4 measured at the M1 visit of Maintenance Phase.

[13] Pituitary MRI at Baseline only for CD subjects and if not done in prior 6 months

Time and Events Schedule															
Assessments	**Screening Phase**		**Dose Titration Phase[1]**			**Maintenance Phase[2]**							**Extended Evaluation Phase[3]**		**FU Visit[4]**
	Scrn[5]	**Baseline[6]**	**DL1 (DL0)**	**DL2 DL3**	**DL4 DL5 DL6 DL7**	**M 1**	**M 2**	**M 3**	**M 4**	**M 5**	**M 6**	**End of MP**	**M 9**	**M 12**	
OGTT (pre-diabetics only)		X							X			X	X	X	X
Dexamethasone Suppression Test (DST)		X[14]													
Serum cortisol		X	X	X	X	X	X	X	X	X	X	X	X	X	X
ACTH		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum lipid measurements, triglycerides		X	X	X	X	X	X	X	X	X	X	X	X	X	X
CRP		X	X	X	X	X	X	X	X	X	X	X	X	X	X
IGF-1		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Spot urine for albumin/creatinine ratio		X													
Spot urine for albumin/creatinine ratio (If abnormal at Baseline)									X			X	X	X	X
Serum testosterone, free/total		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Baseline signs & AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CushingQoL questionnaire		X							X			X	X	X	X
BDI-II instrument		X							X			X	X	X	X
24-h UFC/free cortisol/creatinine/ urinary volume (4 collections)		X										X			
24-h urinary free cortisol/creatinine/ volume (2 collections)							X	X	X	X	X		X	X	X
24-h urinary free cortisol/creatinine/ volume (2 to 4 collections) [15]			X [11]	X [11]	X [11]										
Pharmacokinetic sampling			(X) [16]	(X)[12]	(X)[12]	(X)[12]	(X)[12]	(X)[12]	(X)[12]	(X)[12]	(X)[12]				

[14] DST will need to be available at Baseline if not previously performed and results available within the 2 months prior to start of Screening Phase

[15] First 24-hour urine collection will be Day 10 (±1 days) followed by the second 24-hour collection (ideally on two consecutive days) after start of each dose level. If UFC ≤ULN, there will be 2 additional 24-hour urine collection to confirm UFC results.

[16] Each subject will provide PK samples from at least 2 dose levels during their participation in the study. The sample collection time and the dose level will vary from subject-to-subject and will be determined by the Investigator. See Section 6.2.8.1 for details.

APPENDIX B LABORATORY ANALYTES

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

Hematology

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

Clinical Chemistry

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

Urinalysis

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

Other analytes

HIV Hepatitis B and C antibodies	HbA1c
Serum lipid measurements to include: total cholesterol, LDL, HDL, LDL:HDL ratios, Triglycerides	Serum testosterone (both men and women) FSH (women only) Pregnancy test (urine, women only)
Serum CRP	Urinary free cortisol and total creatinine and total volume on 24-hour urine collections
Spot urine for albumin/creatinine ratio—if normal at Baseline, no further testing required throughout the study	Serum cortisol Serum ACTH
Serum TSH/free T4	INR/PT/PTT
IGF-1	

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 will be completed for each subject who is enrolled in the study. Subject numbers will be assigned by the eCRF system immediately following the performance of 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 Food and Drug Administration (FDA) or a competent regulatory authority is notified.

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

Monitoring and Quality Assurance

During the course of 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 according to 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 which 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 the course of 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 the review of the contents will be in compliance 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 according to 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 the aforementioned 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, Archiving of Study Documentation).

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

APPENDIX E PUBLICATION POLICY

All data generated from this study are the property of Cortendo Inc. and shall be held in strict confidence along with all information furnished by Cortendo. Independent analyses and/or publication of these data by the 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. Authorship will be determined by mutual agreement. For multicenter studies it is mandatory that the first publication is based on data from all centers, analyzed as stipulated in the protocol and not by individual Investigators. Investigators participating in multicenter studies agree not to present data gathered from one center or a small group of centers before the full publication, unless formally agreed to in writing. Written permission to Investigators to publish results will be contingent on review by Cortendo of the methodology and statistical analyses and any publication or presentation will provide for nondisclosure of Cortendo confidential or proprietary information. In all cases, the parties agree to submit all manuscripts or abstracts to all other parties at least 60 days prior to submission. This will enable all parties to protect proprietary information and to provide comments based on information that may not yet be available to other parties.

Further details on the publication process are 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 as a separate document. 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

Conditions Associated with Hypercortisolism in the Absence of 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
- Glucocorticoid resistance
- Morbid obesity
- Poorly controlled diabetes mellitus

Unlikely to have any clinical features of CS

- Physical stress (hospitalization, surgery, pain)
- Malnutrition, anorexia nervosa
- 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 fasting glucose, HbA1c, or 2-hour postprandial glucose during a 75-gram oral glucose tolerance test (GTT). For purposes of this study, however, the diagnosis of prediabetes will be limited to a single prediabetes category of impaired fasting glucose, as follows:

Prediabetes is defined by a fasting glucose of ≥100 mg/dL (5.6 mmol/L) and <126 mg/dL (7.0 mmol/L) (after no caloric intake for at least 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:

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

OR

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

OR

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

OR

4. A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (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 7 Classification of Blood Pressure Levels for Adults >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 8 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 9 through **Table 17** provide examples of drugs that are **PROHIBITED** for concomitant use in COR-2012-01. **Table 18** through **Table 20** provide examples of drugs that **REQUIRE PERMISSION** from the study Medical Monitor prior to concomitant use.

Drugs listed below are categorized into one drug-interaction category per drug; however, some drugs could have been categorized into multiple drug-interaction categories (e.g. dexamethasone is both a systemic corticosteroid and a strong CYP3A4 inducer). In such cases, the drug is categorized into the most restricted concomitant use category as applicable.

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 COR-003, the lists intentionally omit some medications that should not be used concomitantly with COR-003, 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 COR-003 and other medications. Therefore, they should be regarded as a minimum set of excluded and precautioned concomitant medications.

A. Prohibited concomitant medications

Table 9 Steroidogenesis Inhibitors and Systemic Corticosteroids (Interferes with study drug assessment; must be avoided or washed out prior to Baseline Visit)

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

Table 10 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 11 Synthetic progestins that bind with moderate to high affinity[17] to glucocorticoid receptor (GR) or mineralocorticoid receptor (MR) (Interferes with study drug assessment and/or influence underlying signs/symptoms of disease; must be avoided or washed out)

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

Table 12 Somatostatin analogs (Interferes with study drug assessment and/or influence underlying signs/symptoms of disease; must be avoided)

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

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

Table 13 Weight Loss Medications (Interferes with endpoints assessment; must be avoided or washed out)

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

Table 14 Drugs Predicted to Interfere with the Absorption of COR-003 (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

Note on Drug-drug Interactions via CYP3A4

COR-003 is a substrate and potent inhibitor of CYP3A4. Therefore, the following drug interactions may occur when COR-003 is co-administered with other drugs that interact with CYP3A4.

- COR-003 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 COR-003 is prohibited for drugs known to present a risk of serious side effects with increased exposure** (Table 15).
- 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 COR-003 by induction or inhibition of CYP3A4 or by altering absorption are prohibited (Table 16).

The following drug interaction checker may be useful. However, this checker will not supersede the protocol excluded medications lists nor the judgment of the Medical Monitor or delegate: http://reference.medscape.com/drug-interactionchecker

Table 15 Drugs Whose Systemic Exposure is Predicted to be Significantly Increased by COR-003 (via CYP3A4 inhibition; must be avoided or washed out)

Systemic exposure to these drugs is potentially increased **significantly** by the addition of COR-003**; must be avoided**	
Alprazolam, midazolam, triazolam	HMG-CoA reductase inhibitors: atorvastatin, lovastatin, simvastatin, (**NOT** pravastatin, fluvastatin and rosuvastatin)
Cisapride	
Dofetilide	
Eplerenone	
Ergot alkaloids (ergotamine, dihydroergotamine)	Pimozide
Quinidine	Nisoldipine

Table 16 Drugs That Are Predicted to Reduce (Top) or Increase Significantly (Bottom) the Plasma Concentration of COR-003 via CYP3A4 Induction or Inhibition, Respectively and Are Prohibited; must be avoided

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 17 Drugs that can Cause QTc Prolongation (Must be avoided, unless no acceptable alternative is available; permission prior to use required)

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

B. Concomitant medications that require prior permission to be used

Table 18. Drugs Whose Systemic Exposure is Predicted to be Increased Moderately by COR-003

Systemic exposure to these drugs is predicted to be increased by COR-003: 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 19 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 20 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 TO BE CONSIDERED FOR RISK MANAGEMENT

Disease	Symptoms	Signs	Laboratory values
Adrenal Insufficiency	Fatigue/Tiredness/Malaise Weakness Anorexia Nausea Vomiting Constipation Abdominal pain Diarrhea Headache Salt 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

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

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

6. **Menstrual abnormalities (females only):**

   A. **Irregular menstruation:** **None** **Mild** **Moderate** **Severe**

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

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

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

In addition, the following physical signs of CS will be quantified by the Investigator using specific grading systems included in the SPM:

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

Name of Investigator completing assessment (Printed)_____

Signature of Investigator completing Assessment_____

Date_____

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

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