SPONSOR:

CORTENDO AB

PROTOCOL NUMBER:

COR-2012-01

STATISTICAL ANALYSIS PLAN
(Text)

Author:	Jean-Luc Beffy
Version:	Version 1.0
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1 Cover and Signature Pages

Sponsor:	Cortendo AB (a subsidiary of Strongbridge Biopharma plc)
Protocol Number:	COR-2012-01 Amendment #6 (25-Oct-2016)
Study Title:	An Open Label Study to Assess the Safety and Efficacy of COR-003 (2S, 4R-Ketoconazole) in the Treatment of Endogenous Cushing's Syndrome
Document Version No	Version 1.0

We, the undersigned, confirm that we have read, understood and agree to the content of this document and hereby authorize its approval.

Name Title, Organization	Signature	Date
Jean-Luc Beffy Principal Statistician Cmed		19 JUN 2018
Sarah Lilley Principal Statistician Cmed		

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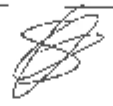
Sarah Lilley Principal Statistician Cmed		20 Jun 2018

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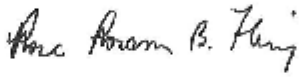
Rosanna Fleming Executive Director, Biostatistics and Data Management, Strongbridge Biopharma plc On behalf of Cortendo AB		19JUN2018
Steve Schoenfeld VP Clinical Research and Development, Strongbridge Biopharma plc On behalf of Cortendo AB		19 JUN 18

Table of Contents

1 List of Abbreviations

ACTH	Adrenocorticotropic hormone
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration time curve
BID	Twice daily
BMI	Body mass index
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
DBP	Diastolic blood pressure
DL*n*	Dose level *number*
DSMB	Data Safety Monitoring Board
DST	Dexamethasone Suppression Test
ECG	Electrocardiogram/electrocardiograph
eCRF	Electronic Case Report Form
FSH	Follicle stimulating hormone
GGT	Gamma-glutamyl transferase
HbA1c	Hemoglobin A1C
HDL-C	High density lipoprotein-associated cholesterol
HR	Heart rate
HRQoL	Health-related quality of life

IC50	Half maximal suppression of urinary free cortisol
ICH	International Conference on Harmonisation
IGF-1	Insulin-like Growth Factor-1
Imax	Maximal suppression of urinary free cortisol
INR	International Normalized Ratio
ITT	Intent-to-Treat
Ka	Absorption rate constant
LDL-C	Low density lipoprotein-associated cholesterol
LFT	Liver function test
LLN	Lower limit of normal
LNSC	Late-night salivary cortisol
LSMEAN	Least Squares Mean
MedDRA	Medical Dictionary for Regulatory Activities
M	Maintenance
MAR	Missing at Random
MRI	Magnetic Resonance Imaging
NCI-CTCAEv4	National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0
OGTT	Oral glucose tolerance test
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PP	Per Protocol
QoL	Quality of life
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected using Bazett's correction
QTcF	QT interval corrected using Fridericia's correction
RBC	Red blood cell
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SBP	Systolic blood pressure

SD	Standard deviation
t½	Half-life
TEAE	Treatment-emergent Adverse Event
TFL(s)	Tables, Figures and Listings
TSH	Thyroid stimulating hormone
UFC	Urinary free cortisol
ULN	Upper limit of normal
V/F	Apparent volume of distribution following oral administration
VAS	Visual analog scale
WBC	White blood cell

2 Introduction

The purpose of this document is to describe the statistical methods, data derivations and data summaries to be employed in the analysis of Study COR-2012-01, An Open Label Study to Assess the Safety and Efficacy of COR-003 (2S,4R-Ketoconazole) in the Treatment of Endogenous Cushing's Syndrome (CS).

The preparation of this statistical analysis plan (SAP) has been based on International Conference on Harmonisation (ICH) E3 and E9 Guidelines and in reference to Protocol COR-2012-01 (version 03, 10 April 2013) and its Amendment 1 (09 September 2013), Amendment 2 (20 October 2013), Amendment 3 (26 February 2014), Amendment 4 (28 August 2014), Amendment 5 (16 April 2015) and Amendment 6 (25 October 2016). In addition, there are also some country-specific versions of the protocol.

The original protocol is dated the 10 April 2013. This current SAP is based on Protocol Amendment 6 (25 October 2016). The handling of the specific endpoints impacted by changes due to Protocol Amendment 5 are also described in relevant sections throughout this document.

Data collected under protocol amendments prior to Protocol Amendment 5 and 6 but no longer required as per Protocol Amendment 5 and 6 will be listed but not summarized.

Subjects were consented to start the study under Protocol Amendment 2 onwards. Subjects originally consented prior to Protocol Amendment 6 were re-consented for Protocol Amendment 6, or earlier if applicable.

Discontinuations from the study are discussed in Section 6.2 (definitions of Dose Titration Phase and Maintenance Phase), Section 6.6.3 (Partial and missing dates for Adverse Events / Clinical Signs and Symptoms of CS) and Section 8.4 (Subject Disposition).

3 Study Objectives

3.1 *OBJECTIVES*

Primary objectives:

- 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 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 in mean 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 mean 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 mean 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 (LNSC) 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 (BDI-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 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 LNSC 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 BDI-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 ≤ 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 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 Objectives:

- 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 (AESIs) such as QT corrected for heart rate (QTc), if data allow;
- To explore the dose-response relationship for reduction of UFC levels if data allow.

3.2 *ENDPOINTS*

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 LNSC 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 BDI-II after 3 and 6 months of dosing in the Maintenance Phase;
- Change from Baseline in CS comorbidities biomarkers (fasting glucose, hemoglobin A1C (Hb1Ac), systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol, low and high density lipoprotein-associated cholesterol [LDL-C, HDL-C, 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 as described further below.

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 LNSC 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 BDI-II after 9 and 12 months of dosing (Extended Evaluation Phase);
- Change from Baseline in CS comorbidities biomarkers (fasting glucose, HbA1c, SBP, DBP, total cholesterol, LDL-C, HDL-C 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 in the Extended Evaluation Phase. Clinical Benefit is defined as follows:
  1. UFC response as indicated by UFC ≤ ULN, and
  2. No increase of 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 (Section 6.7.2) and
4. 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 and at 12 months in the Extended Evaluation Phase.

Safety Endpoints:

- Incidence and severity of TEAEs, including serious TEAEs, and TEAEs of special interest.
- Changes from Baseline in safety laboratory parameters (hematology, chemistry, urinalysis, coagulation) and incidence of abnormal laboratory parameters results at each post-baseline visit in the Maintenance Phase;
- Changes from Baseline in biomarkers and hormone laboratory parameters (Thyroid stimulating hormone [TSH], Free T4, Adrenocorticotropic hormone [ACTH], Insulin-like Growth Factor-1 (IGF-1) and testosterone concentrations) and incidence of abnormal laboratory parameters results at each post-baseline visit in the Maintenance Phase;
- Changes from Baseline in vital signs (SBP, DBP, heart rate [HR], and body temperature) and incidence of abnormal vital signs (SBP, DBP, and HR) at each post-baseline visit in the Maintenance Phase;
- Changes from Baseline for quantitative electrocardiogram (ECG) parameters, including QTc interval, from centrally read ECGs and incidence of abnormal QTc intervals at each post-baseline visit in the Maintenance Phase;
- Changes from Baseline in pituitary tumor size, among subjects with Cushing's disease (CD) at Baseline, assessed by central reading of magnetic resonance image (MRI) at 6 months in the Maintenance Phase.

Pharmacokinetic Endpoints and Pharmacokinetic/Pharmacodynamic Modeling

- The following will make use of PK samples collected during the Dose Titration and Maintenance Phases:
    - Estimate the following parameters using population PK modeling: apparent clearance following oral administration (CL/F), apparent volume of distribution following oral administration (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.

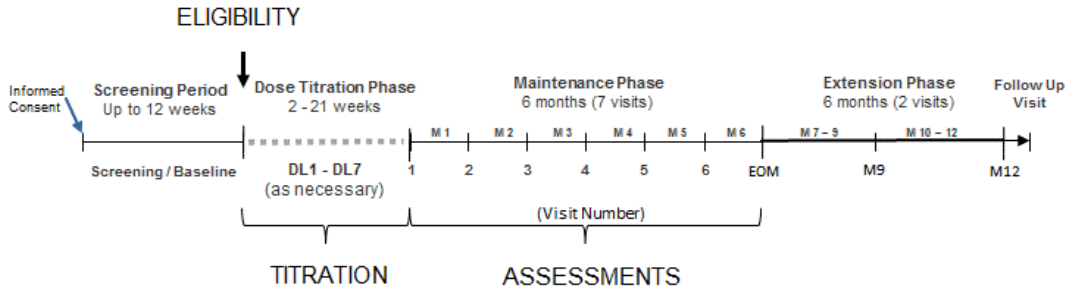
4 Study Design

4.1 *STUDY DESIGN AND POPULATION*

This study is the first clinical study investigating the safety and efficacy of COR-003 in subjects with endogenous Cushing´s Syndrome (CS). Endogenous Cushing´s syndrome (CS) is a rare but serious and potentially lethal endocrine disease caused by chronic elevated cortisol exposure to human organs.

This study is a single arm, non-randomized, 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.

Figure 1. Study Design



Following an initial screening and washout period, this study will be conducted in 3 study 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 Dose Titration Phase;
- Extended Evaluation Phase: 6 months of continued treatment after the Maintenance Phase.

Approximately 90 subjects that meet eligibility criteria and sign informed consent will be enrolled into the Dose Titration Phase of the study to ensure that at least 70 subjects complete the 6-month assessment period in the Maintenance Phase of the study.

4.2 *STUDY TREATMENTS AND ASSESSMENTS*

The time and events schedule for the screening, Dose Titration, Maintenance and Extended Evaluation Phases is given in Table 1 in Section 15.1.1.

After signing the informed consent, subjects will enter the Screening Period. After performing initial Screening assessments, subjects on prior CS therapies or other prohibited medications must enter a washout period, as applicable (see Protocol Section 5) before completing all Screening assessments detailed in Table 1. Baseline measurements will be obtained as part of the Screening assessments, after washout and completion of all initial Screening procedures.

All subjects having signed off the informed consent and who meet inclusion criteria (and none of the exclusion criteria) will begin treatment on 150 mg twice daily (BID) (DL1), approximately every 12 hours, and will be dose-titrated approximately every 18 (± 4) days until the Therapeutic Dose is reached.

COR-003 will be administered BID according to the titration scheme in Table 2 (starting at DL1) until one of the following criteria has been met:

- Mean 24-hour UFC levels are ≤ ULN established for the assay being used at a central laboratory,
- Reached the highest protocol-specified dose,
- Reached the highest tolerated dose at the discretion of the Investigator.

Table 2: Dosing Titration Scheme

Dose Level (DL)	Morning Dosing	Evening Dosing	Total Daily Dose	Dose group label
DL0	0 mg	150 mg	150 mg	COR-003 150 mg
DL1	150 mg	150 mg	300 mg	COR-003 300 mg
DL2	150 mg	300 mg	450 mg	COR-003 450 mg
DL3	300 mg	300 mg	600 mg	COR-003 600 mg
DL4	300 mg	450 mg	750 mg	COR-003 750 mg
DL5	450 mg	450 mg	900 mg	COR-003 900 mg
DL6	450 mg	600 mg	1050 mg	COR-003 1050 mg
DL7	600 mg	600 mg	1200 mg	COR-003 1200 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				

Titration rules and adjustment criteria:

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 BID, taken as one tablet in the morning and one tablet in the evening. Decisions for subsequent dose increases will be based on each subject's drug tolerability, assessment of UFC levels and safety data and will be made by the Investigator. The approximate interval between dose adjustments will be 18 (±4) days.

All subjects will be asked to collect two adequate 24-hour urine specimens starting at approximately Day 10 (±1 day) after the start of each dose level, ideally on two consecutive days. Urine volume and creatinine will be measured as a marker of the adequacy of each collection (Section 6.7.1). 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. 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). Based on their UFC results and tolerability, subjects will be asked to return 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; Protocol Section 4.2.1.1); or

- Enter the Maintenance Phase (if an alternative determination of Therapeutic Dose of COR-003 has been made; Protocol Section 4.2.1.1) as applicable.

Determination of the effective and tolerable dose of COR-003 (Therapeutic Dose):

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 was achieved 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).
- 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) [Protocol 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 UFC partial response from Baseline, the subject may enter the Maintenance Phase at that dose level.
- If the subject has reached the highest <u>tolerated</u> 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 UFC 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 liver function tests (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 UFC 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.

Dose Titration to the Therapeutic Dose:

Subjects will continue the process of dose titration until the Therapeutic Dose has been reached (Protocol 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, during Dose Titration Phase at each dose level within approximately 1 to 2 hours after drug administration (i.e., at ~ Cmax), 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 up to 5 minutes of continuous ECG (see Protocol 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.
- If the subject develops signs and/or symptoms of adrenal insufficiency (e.g., orthostatic hypotension, nausea, vomiting, and/or abdominal pain), based on further investigation (see Protocol 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 Protocol 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.

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 Table 1. Subjects will be advised to contact the Investigator immediately in the event of developing adrenal insufficiency (see Protocol 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 Protocol 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 Protocol Section 4.2.1.1).

Maintenance Phase:

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 two weeks of the first UFC samples for analysis 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 Protocol Section 5.3.2., instructions for re-challenge), QTc prolongation (Protocol Section 5.3.1) and adrenal insufficiency (Protocol 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.

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 (Protocol Section 4.5).

Exclusion of Treatment Effect Due to Delayed Onset of Radiation Therapy (Protocol Section 4.4.1):

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 (Protocol 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.]

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 three 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 Table 1.

After completion of treatment in this study, if subjects do not extend treatment through the expanded access program (Protocol Section 4.7), they will return for a Follow-Up Visit as indicated in Table 1. 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 or into another Phase 3 study with COR-003 (see Protocol Section 4.7 and Protocol COR-2017-01, also known as LOGICS)].

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 Protocol Section 5.3.1 at 150 mg/day
- LFT abnormalities as specified in Protocol Section 5.3.2
- Adrenal insufficiency at the lowest dose of COR-003 (150 mg daily)—See also Protocol Section 6.3.3 for more details
- Any withdrawal criteria specified in Protocol Section 5.3.

Subjects who are withdrawn early will complete the Follow-Up Visit (see Table 1) 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.

Optional Expanded Access Program and Open Label Extension Studies:

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 directly into expanded access program will NOT be required to complete the Follow-Up Visit for COR-2012-01.

The Sponsor is planning an open label extension study that will be open to subjects who complete visit M12 in COR-2012-01 (Study COR-2017-OLE, also known as OPTICS). The study protocol for the open label extension study is in development as of the writing of this SAP. If subjects continue directly into OPTICS, they will NOT be required to complete the Follow-Up Visit for COR-2012-01.

The Sponsor is implementing a double-blind, randomized withdrawal following open label therapy study to assess the safety and efficacy of COR-003 (Study COR-2017-01, also known as LOGICS). This study is open to subjects who complete visit M12 in COR-2012-01. If subjects continue directly into LOGICS, they will NOT be required to complete the Follow-Up Visit for COR-2012-01.

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 Table 1.

4.3 *RANDOMIZATION, BLINDING, AND DATA INTEGRITY*

This is a non-randomized study. All subjects that meet eligibility criteria and sign informed consent will begin treatment on 150 mg BID in the Dose Titration Phase.

Although the study is open-label, access to much of the data is restricted to certain team members to minimize bias introduction prior to the Maintenance Phase (i.e. primary efficacy endpoint) database lock. Details are provided in the "Data Restriction Plan (currently Version 1.0, September 2016)". The following description includes elements of this plan; however, the Plan stands alone as the complete and definitive description of data restrictions on the study prior to database lock. If the Data Restriction Plan is amended subsequent to the finalization of this SAP, then the amended Plan will supersede the current version of the Plan.

Dummy data will be used for programming Tables, Figures and Listings (TFLs) containing restricted data prior to the Maintenance Phase database lock. Restricted data are summarized in Table 3.

One or more dry runs (i.e. creation of data outputs prior to the Maintenance Phase database lock to review the outputs, layout and derivations) using dummy data will be performed.

Refer to Section 9 for details regarding the timing of the two planned database locks and analyses, one at the end of the Maintenance Phase and one at the end of the Extended Evaluation Phase, including the Follow-up visits.

Table 3: Restricted Data

Variable	Data Captured	Reason for Restriction
UFC	Includes 24-hour UFC and UFC adjusted for urine creatinine	Primary efficacy endpoint (and some secondary endpoints)
LNSC results	Cortisol concentration	Secondary efficacy endpoint
PK*	All measures of blood concentration of study drug(s) for PK analyses	PK believed directly related to clinical efficacy of study drug
Serum Cortisol	Cortisol concentration	Secondary efficacy endpoint
Standardized Photo Assessments	Subject photographs, all views	Signs of hypercortisolism (i.e., visual assessment of the disease)
Disease Comorbidity biomarkers	Includes concentrations of fasting glucose, HbA1c, lipids (total C, LDL-C, HDL-C, triglycerides and LDL-HDL-C ratio), CRP, body weight and urine microalbumin to creatinine ratio	Secondary efficacy endpoints
Cushing QoL questionnaire+	All data collected using the Cushing QoL instrument	Secondary efficacy endpoint
BDI-II instrument+	All data collected using BDI-II	Secondary efficacy endpoint
Cushing's Clinical Signs and Symptoms+	All data collected using the Signs and Symptoms assessment questionnaire	Secondary efficacy endpoint
Dose level and compliance+	Data pertaining to dispensed dosage of study drug, including disclosure of dose-level, dose changes, and compliance with study medication	Dose level will only be restricted when combined with other **Restricted Data** in this table. Data summaries produced prior to database lock for the general study team will not display dose levels.

+ These data will not be restricted in the clinical database. However, programming conducted prior to clinical database lock will use dummy data generated by the restricted programming team.

* Except by the medical monitor or designee for purposes of evaluating an adverse event (AE) report.

4.4 *SAMPLE SIZE JUSTIFICATION*

A sufficient number of subjects (estimated at approximately 90) will be enrolled into the Dose Titration Phase of the study assuming that at least 70 subjects complete the 6 months Maintenance Phase. The approximately 90 subjects to be enrolled in the Dose Titration Phase will be the primary analysis population (i.e. the intent-to-treat [ITT] population; see Section 7). Table 4 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 under these sample size assumptions. 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 4: One Sample χ2 Test: Null Hypothesis 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

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. Table 4 in Protocol Section 12.3 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.

For more detail on the sample size justification see Protocol Section 12.3.

5 Statistical Considerations

The SAS system, version 9.3 (or higher), will be used for all analyses, unless otherwise specified.

5.1 *HYPOTHESIS TESTS*

Details on hypothesis tests are provided in Section 5.4.

5.2 *DEFINITIONS OF DOSE GROUPS*

Throughout the document,

- The expression "dose group" refers to a group of subjects who were receiving a given dose level (DL0 through DL7) as of the dates of their entries in the Maintenance Phase. The subject's dose at the start of the Maintenance Phase is also referred to as the subject's Therapeutic Dose. Subsequent dose adjustments that may have been made after a subject's entry date into the Maintenance Phase do not change membership in a subject's primary dose group.
- There are three exceptions to use of this general definition: The first exception is made for subjects who never enter the Maintenance Phase of the study (for any reason); the second exception is for summaries that are limited to the Dose Titration Phase (i.e. the summary does not include Maintenance Phase assessments and thus does not include doses at entry into the Maintenance Phase); the third exception is for summaries made for the final database lock at the end of the study (i.e. after the last subject has completed the Extended Evaluation Phase) that include subjects who enter the Extended Evaluation Phase. Summaries by dose group in these three exceptions are defined immediately below.
- Exceptions 1 and 2 as above: Summaries by dose for subjects who do NOT enter the Maintenance Phase and summaries limited only to the Dose Titration Phase will use the following conventions:
    - For summaries of AEs and concomitant medications, the AEs and concomitant medications will be summarized by the last dose received on or before the AE or concomitant medication started.
    - For the summary of disposition in the Dose Titration Phase, subjects will be summarized by the last dose received in the Dose Titration Phase.
    - For summaries of demographics and Baseline characteristics, medical history and disease characteristics, prior medications, and prior CS therapy for the ITT population, subjects who do NOT enter the Maintenance Phase will be summarized by the last dose received in the Dose Titration Phase.
    - For summaries of any other parameter/variable in the Dose Titration Phase, the results will be presented by dose level, not by-visit. Refer to Section 6.3 for details.
    - For other summaries, specific rules will be provided in the relevant sections.

- Exception 3 as above: Because the protocol provides for dosage adjustments during the Extended Evaluation Phase, in the final analysis (i.e. after last subject completes the final study visit), summaries by dose for subjects who enter the Extended Evaluation Phase will use the following conventions:
    - For assessments collected by visits, subjects will be summarized by the dose they received at the previous visit;
    - For the summary of disposition in the Extended Evaluation Phase, subjects will be summarized by the last dose received in the Extended Evaluation Phase.
    - For all other summaries, subjects will be included in the dose group corresponding to the last dose they received on or before the relevant assessment or event.
- The "All dose groups combined" includes all subjects regardless of their dose group, as defined above.

5.3 *DATA PRESENTATION*

- **Page Orientation**: Landscape
- **Post-text outputs**, will be generated in lst and converted to rtf. Figures will be generated directly in .rtf format. All the outputs will also be generated in .pdf format.
- **Font**: Courier New font with minimum of 9-point font size
- **Margins**: top: 3/8", bottom: 3/8", left: 3/4" and right: 3/8" on Letter paper
- **Alignment:** Columns header will be left aligned.
- **Dose level designations**:
    - Dose level designation labels will be as described in the last column in Table 2 in Section 5.2. The All dose groups combined will be labeled as "All Subjects" in the tables.
    - For the Dose Titration Phase, subjects will generally be summarized under the different doses they received during that period, with some exceptions (see Section 6.2 for details).
      If there is only one subject who received 150 mg dose, then there is no need for a '150 mg' column in the Dose Titration Phase tables. The subject's data at that dose will just be displayed in the listings, and this decision will be documented in the Clinical Study Report.
    - For the Maintenance Phase, subjects will be summarized under the dose they received at the beginning of the Maintenance Phase . If the subject did not reach the Maintenance Phase and is included in the summaries and analyses for the ITT Population (Section 7) (i.e., summaries and analyses of UFC response and UFC improvement rates), the subject will be summarized under the last dose the subject received in the Dose Titration Phase.

    - For the Extended Evaluation Phase, subjects will be summarized under the most recent dose level received (see Section 6.2 for details).
- **By-phase table layouts:** Because the number of subjects who received each dose level is different for each phase, assessments that occur in more than one study phase will be summarized in the following way:
    - The Dose Titration Phase will not be summarized by visit, only by dose level.
      If a subject has more than one assessment of mean UFC at the same dose level during the Dose Titration Phase, then the average of the mean UFC results will be included in the summaries on the mean UFC, UFC response and UFC improvement.
      If a subject has more than one assessment of any other parameter/variable than mean UFC at the same dose level during the Dose Titration Phase, then the worst-case result will be included in the summary. The determination of the worst-case results for a subject at a dose level will include all results (including those from unscheduled visits) while at that dose level under consideration. Refer to Appendix 15.2 for determining which results are considered the worst results for other laboratory parameters, vital signs and ECG parameters.
      All results will be included in the listings, and where applicable the worst-case result will be flagged. The N for each dose level will be the number of subjects who received the given dose level at any time during the Dose Titration Phase.
    - The Maintenance Phase will be summarized on a separate page, by visit and dose level. The N for each dose level will be the number of subjects receiving the given dose level at the beginning on the Maintenance Phase (i.e., the Therapeutic Dose).
    - The Extended Evaluation Phase and Follow-up visit will be summarized on a separate page, by visit and dose level. The N for each dose level will be the number of subjects who received the dose level at any stage during the Extended Evaluation Phase. For all summaries of the Extended Evaluation Phase the number of subjects who received the dose level at the given visit will also be presented.
    - The Screening/Baseline visit or period will be presented for each by-phase table.
- **Visit labels** for the visits for all study phases are displayed in Table 5 below.

Table 5: Visit labels

Study Phase	Period (per the Protocol)	Tables, Figures and Listings Label
Screening / Baseline	Historical Data	
	Screening/ Baseline	BAS
Dose Titration Phase	All	DT

Study Phase	Period (per the Protocol)	Tables, Figures and Listings Label
Maintenance Phase**	Month 1*	M1 (D1)
	Month 2	M1 (D30)
	Month 3	M2 (D60)
	Month 4	M3 (D90)
	Month 5	M4 (D120)
	Month 6	M5 (D150)
	End of Maintenance Phase	M6 (D180)
Extended Evaluation Phase***	Month 9	M9
	Month 12	M12
Follow-up	Follow-up	FU

* In protocol versions prior to Amendment 5, this visit was labelled Month 0. The time window did not change, only the label. For analysis, Day 1 of Month 1 in the Maintenance Phase will be labelled 'Month 1' regardless of the protocol version.

** As per protocol Amendment 6, time window is considered as (30 ± 7 days) for each visit during the Maintenance Phase after Month 1 visit.

*** As per protocol Amendment 6, time window is considered as (90 ± 14 days) for each visit during the Extended Evaluation Phase.

- **Repeated Screening assessments:** Where the subject has been re-screened, or had repeat assessments during the Screening period (Section 6.4), the last value prior to first dose will be summarized.
- **Nominal visits, post-baseline**: Nominal visits will be defined as the assessment(s) closest to the planned visit day and within the visit window (see Appendix 15.3) Nominal visits will be used in the summary, analysis and graphical representation of the data.
    - For UFC, depending on the visit considered, 2 to 4 samples are collected. All adequately collected samples (see Protocol Section 6.2.6.1) within the visit window will be used to derive the mean.
    - SBP, DBP and abdominal girth are measured in triplicate and for each, the endpoint is defined as the mean of those 3 measures. Therefore, for each assessment, only those performed on the same day will be used for the derivation of the endpoint. For each endpoint, if there is more than one mean value within a visit window that is equally distant from the nominal visit, the last calculated mean will be flagged for analysis. If there are more than 3

assessments on the same day, the repeat and unscheduled assessments will not be used to derive the mean.

- LNSC, depending on the visit considered, may be collected for 2 nights at a visit (see Table 1). When this occurs, the mean LNSC will be derived and analyzed. A LNSC sample is adequate if there is no comment associated to the sample which specifies that it is not adequate. If there are more than 2 adequate samples available within 4 days, repeat and unscheduled assessment(s) will not be used to derive the mean. If inadequate samples are repeated within the 4 days, up to 2 adequate samples will be used selecting those closest to the scheduled collection time.
- For all other assessments, if there is more than one assessment in the visit window that is equally distant from the nominal visit, the last assessment will be flagged for analysis.

- **Other unscheduled visits or repeat assessments**:
  - All abnormal values detected at unscheduled visits, or not identified as a nominal visit, will be included in shift tables pooled over study phase (see Section 8.11.2, Section 8.11.3, Section 8.11.4, Section 8.11.5).
  - All data, scheduled and unscheduled, will be listed.
- **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.
  - The number of missing values will be presented as a separate category with no percentage, but only if 1 or more subjects have missing data for the summary. Otherwise, all categories will be presented (even if no subjects are counted in the category).
  - Counts of zero in any category will be presented without a percentage.
  - Unless otherwise specified, percentages will be calculated based on the number of subjects in the population.
    - For shifts from Baseline and incidence of abnormalities, percentages will be calculated based on the number of subjects with non-missing results for the assessment and visit (if applicable).
- **Precision of summary statistics**:

  Integer – Sample size (n, N) and number of missing responses (if displayed)

  - One additional decimal place than reported/collected (see Section 10 for laboratory assessments) for mean, geometric mean, median, other percentile, confidence interval (CI)
  - Two additional decimal places than reported/collected for SD
  - Same number of decimal places as reported/collected for minimum, maximum
  - Percentages:
    - <0.1, if the percentage is < 0.1%,

    - Otherwise: one decimal place.
  - P-values presented to the ten-thousandth, except values that are less than the level of precision will be presented as <0.0001. Similarly, large p-values will be presented as >0.9999.
- Data will be presented on listings in order of center, subject, visit, assessment date / time and assessment type / assessment (in order collected on Case Report Form [CRF], unless otherwise specified).
- Relative day calculations will be [date of interest – relative date + 1 (date of interest >= relative date)]. This calculation will result in dates prior to the relative date being presented as negative days, and those occurring on or after the relative date as Day 1 or later, i.e., there will be no Day 0.
- Dates will be presented in format DDMMMYYYY.
- Partial dates will be presented as - -MMMYYYY or - - - - - YYYY.
- All laboratory data results will be received from central laboratories, so no data conversion will be performed, results will be summarized based on the standard international units reported, with one exception. For HbA1c, the values will be summarized in tables and figures in conventional unit, ie, as %. The HbA1c values will be presented in the listings in both conventional and international units.
- For results reported as '<' or '>' the result just below or just above (using the precision for the lab test) will be analyzed (i.e. if the result is < 5.0, then it will be summarized as 4.9, if the result is > 5200 then it will be summarized as 5201).
- Dictionary names and versions will be included in the footnotes of the AEs and medications tables and listings.
- **Source footnotes:** Each table will have a footnote that lists the source data listing(s). Each figure will have a footnote that lists the source tables(s), if available, or the source data listing(s), otherwise.
- Minor deviations between template and actual data display are acceptable. For example, changes in numbering or title, modifications or additions to footnotes for clarity, or minor differences in appearance should not be considered deviations from the TFL shells. Further changes in the templates may occur after review of the dry runs prior to the Maintenance Phase database lock.

5.4 *DEFINITIONS*

- **Baseline** is defined on an assessment level as the last value/result where assessment date is less than the date of first study treatment, unless otherwise specified. For UFC and LNSC all adequate samples within the visit window and prior to the first dose of treatment will be considered to derive the Baseline mean.
- **Screening / Baseline period**: all assessments performed strictly prior to the first dose of study drug administration. Results from assessments collected at Screening and/or Baseline visits will not be summarized separately, but the Baseline results (defined above as the last non-missing result prior to the first dose of study drug administration) will be summarized (if applicable) on all tables unless otherwise specified in the TFLs shell document.

- **Dose Titration Phase**: all assessments performed between the first dose date up to (and including) the first visit after the Investigator has determined that the subject has reached their Therapeutic Dose (referred to as M1 (D1)) or the date of discontinuation if the subject discontinued prior to the Maintenance Phase.
- **Maintenance Phase**: all assessments performed between the day after the M1 (D1) visit up to (and including) the last assessment date at the End of Maintenance Phase or the last date of data collection if the subject discontinued prior to the End of Maintenance Phase.

For a subject who completed the Maintenance Phase, the assessment considered for the analysis of the last assessment in the Maintenance Phase will be defined as the assessment(s) closest to the planned Month 6 visit day (D180) and within the visit window allowed for Month 6 visit.

For a subject who withdrew during or at the end of the Maintenance Phase, the assessment considered for the analysis of the last assessment in the Maintenance Phase will be defined as the assessment(s) closest to the planned day of the last assessed nominal visit in the Maintenance Phase and within the visit window allowed for that last assessed nominal visit.

For a subject who withdrew during or at the end of the Maintenance Phase, the data from the Follow-up visit (if performed) may be included in the summaries for the Maintenance Phase based on the visit windows specified in Appendix 15.3.

- **Extended Evaluation Phase**: all assessments performed between the day after the last assessment performed at the End of the Maintenance Phase visit up to (and including) the date of completion of the last visit of the Extended Evaluation Phase or the last date of data collection if the subject discontinued at any time during the Extended Evaluation Phase. For subjects who withdraw during the Extended Evaluation Phase, the data from their Follow-up visit (if performed) may be included in the summaries for Extended Evaluation Phase based on the visit windows in Appendix 15.3.
- **TEAE**: Any AE that started on or after the date of first dose or that worsened in intensity after the first dose of treatment and started prior to or on the last dose date + 30 days. If the start time of the AE is known, it will be used to determine whether the AE is a TEAE or not. Otherwise, if the AE started on the day of the first dose or started prior to the first dose and worsened (increased in intensity, became related to the study drug and/or became serious AE [SAE]) on or after the day of first dose it will be categorized as a TEAE. For subjects who withdraw during or at the end of the Dose Titration Phase, any reported AE that starts after withdrawal but within 30 days of their last dose will be included in the summaries for the Dose Titration Phase. For subjects who withdraw during or at the end of the Maintenance Phase, any reported AE that starts after withdrawal but within 30 days of their last dose will be included in the summaries for the Maintenance Phase. For subjects who enter the Extended Evaluation Phase, any reported AE that starts within 30 days after the last dose will be included in the summaries for the Extended Evaluation Phase.
- **N**: Number of subjects in the population and dose group, regardless of the study phase.
- **Dose increase during the Maintenance Phase**: is defined as any dose increase above the Therapeutic Dose the subject received at the beginning of the Maintenance Phase recorded in the Dose Adjustment electronic CRF (eCRF) page during the Maintenance Phase. If the

dose was reduced during the Maintenance Phase due to any reason and then increased to the Therapeutic Dose it is not considered as a dose increase.

5.5 *STATISTICAL ASSUMPTIONS*

The primary analysis of the primary endpoint for this study will be the proportion of clinical responders (ie, a reduction in mean 24-hour UFC levels to ≤ULN) to COR-003 in the ITT population, following 6 months of dosing in the Maintenance Phase without a dose increase during that phase.

As stated above, subjects who had a dose increase above the Therapeutic Dose at any time during the Maintenance Phase will be considered non-responders.

Withdrawn subjects prior to the End of the Maintenance Phase visit assessment will be considered non-responders. These include subjects in the ITT population who did not enter the Maintenance Phase (i.e., the DT population). All other subjects who have missing mean UFC at M6 [D180] for any other reason, including insufficient number of adequate samples, will also be considered non-responders at M6 [D180].
Additionally, subjects who previously received radiation therapy and who exhibited no rebound increase in the first assessment of mean 24-hour UFC levels following withdrawal of COR-003 immediately after the end of the Maintenance Phase (i.e. mean 24-hour UFC levels ≤ ULN) will be considered non-responders. For the subjects who previously received radiation therapy and achieved clinical response at the End of the Maintenance Phase, the first assessment of mean 24-hour UFC levels following withdrawal of COR-003 immediately after the end of the Maintenance Phase will be calculated if there are at least two adequate 24-hour urine samples collected at least 14 days after the end of the Maintenance Phase visit and before the drug intake is resumed. If there is only one adequate sample that qualifies for such a subject, then the mean 24-hour UFC levels will be missing and the subject will be considered a non-responder. If the subject stopped the treatment intake for less than 14 days after the End of the Maintenance Phase visit and had at least two adequate 24-hour urine samples collected during that period so that the mean 24-hour UFC levels was available for that subject, then the subject will be considered a responder if the mean 24-hour UFC levels > ULN (i.e. the subject rebounded in that period) and a non-responder if the mean 24-hour UFC levels ≤ ULN (conservative approach).

The proportion of responders in the ITT population will be estimated along with its corresponding two-sided 95% 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 null hypothesis will be rejected if the lower bound of the two-sided CI is greater than 20%. The hypothesis test was planned to have 90% power with two-sided 5% Type I error, if the alternative response was 35%.

Multiplicity adjustment:

All secondary efficacy endpoints will be analyzed; however, statistical inferences for the secondary endpoints will be made only if the primary objective is met.

For each of the 8 CS comorbidities biomarkers (fasting glucose, Hb1Ac, SBP, DBP, total cholesterol, low and high density lipoprotein-associated cholesterol [LDL-C, HDL-C, respectively], and body weight), the primary analysis will be the analysis of the change from Baseline to the End of Maintenance Phase (Month 6 [Day 180]) visit (or to the last assessed visit of the Maintenance Phase). The formal statistical testing will only be performed for this primary analysis. The null hypothesis to be tested for each of the 8 CS comorbidities biomarkers is if the mean change from Baseline at the End of Maintenance Phase is at most 0 versus the alternative hypothesis that the mean change from Baseline is greater than 0. Given there will be a total of 8 statistical tests, the statistical significance level will be adjusted using the Hochberg method [4], controlling the family-wise error rate at 5%.

Each of the other secondary efficacy endpoints will be analyzed using two-sided tests with an alpha level of 5%. The type I error will not be adjusted for multiplicity testing of these other secondary endpoints.

Some exploratory efficacy endpoints for the Extended Evaluation Phase will be analyzed through 95% CI and/or statistical tests, but the resulting CIs and p-values will be used for descriptive purposes only; no statistical inferences will be made.

Some safety endpoints will be analyzed using two-sided tests with a 5% alpha level. The tests are for safety signal detection rather than formal hypothesis testing; no statistical inferences will be made. Interpretation of safety results, when possible, will be made based on the pattern of results overall rather than individual assessment results.

The protocol has been amended to define the visit windows to be used to determine the nominal visits (see Section 6.3). Data collected from the assessment(s) that are no longer collected following a protocol amendment will be listed rather than summarized. Data collected from new assessment(s) following protocol amendments will be listed, summarized and/or analyzed only for subjects who have been enrolled under that protocol amendment and subsequent amendments.

5.6 *Imputation Rules*

Following ICH E9, the following imputation methods will be used.

Under the Missing at Random (MAR) assumption, the longitudinal analyses provide an unbiased estimate of the treatment effect that would have been observed if all subjects had continued on treatment for the full study duration.

5.6.1 Urinary Free Cortisol Response and Urinary Free Cortisol Improvement Categorization

See Section 6.7.2 for the definitions of UFC response and UFC improvement. UFC response is referred to as clinical response in the protocol. The term “clinical response” will still be used in the SAP and TFLs to refer to the primary efficacy endpoint, while the term “UFC response” will be used in the SAP and TFLs for the at-visit analysis.

UFC improvement is referred to as complete or partial response in the protocol. The term "UFC improvement" will be used in the SAP and TFLs instead.

Analysis of data for specific visits in the Maintenance Phase will be performed using three different approaches to account for missing data during the Maintenance Phase.

1. At-visit analysis considering dose increase (imputation scheme #1):
    a. For ITT subjects who did not enter the Maintenance Phase: Such subjects will be considered non-responders and non-UFC-improvers at each visit in the Maintenance Phase.
    b. Subjects with a dose increase (see Section 6.4) during the Maintenance Phase will be considered non-responders and non-UFC-improvers for all Maintenance Phase visits after the dose increase.
    c. If mean 24-hour UFC levels are missing for reasons other than a) above, UFC response and improvement will also be missing (i.e. no imputation).
2. At-visit analysis regardless of dose increase (imputation scheme #2):
    a. For ITT subjects who did not enter the Maintenance Phase: Such subjects will be considered non-responders and non-UFC-improvers at each visit in the Maintenance Phase.
    b. For subjects who entered the Maintenance Phase:
        i. If mean UFC is missing at only one visit in the Maintenance Phase:
        - If the mean UFC is missing at a visit Month X, which is before M6 [D180], then the subject will be considered as a responder at Month X if the subject is also a responder/improver at the visit immediately before and the visit immediately after Month X. Otherwise, the subject will be considered as a non-responder/non-improver.
        - If the mean UFC is missing at M6 [D180], then the subject will be considered as a responder at M6 [D180] if the subject is also a responder at M5 [D150] and at the Month 9 visit. Otherwise, the subject will be considered as a non-responder (including the case where the mean UFC at the Month 9 visit is not available).
        ii. If mean UFC data are missing at more than one intermediate visit in the Maintenance Phase or the End of Maintenance Phase (Month 6 [Day 180]): Missing assessments in the Maintenance Phase will be categorized as non-response/non-improvement.
3. At-visit analysis using the worst-case approach (imputation scheme #3)
    a. The worst-case approach assumes that the subject will be systematically considered as a non-responder/non-improver at a given visit of the Maintenance Phase if mean UFC data is missing at that visit regardless of any other consideration (including the case of an ITT subject who did not enter the Maintenance Phase).

The primary analysis for UFC response will be performed as described in Section 6.5.

A first sensitivity analysis will be conducted with the imputation scheme #1.

A second sensitivity analysis will be conducted with the imputation scheme #2, i.e. where dose increase does not negate the response.

Finally, a third sensitivity analysis using the worst-case approach (imputation scheme #3) will be conducted to assess the robustness of the results from the analyses based on the the imputation schemes #1 and #2.

5.6.2 Mean Urinary Free Cortisol and Cushing's Syndrome Comorbidity Biomarkers

Missing values at post-baseline assessments will not be replaced and will be regarded as missing in longitudinal analyses. The longitudinal model will account for missing data for the primary analysis.

5.6.3 Partial and Missing Dates

The following rules will be used when imputing partial or missing dates for reporting purposes, such as defining in which study phase an AE started, or under which visit the Clinical Sign and Symptoms occurred. Imputed dates, unless otherwise specified, will not be presented in data listings.

5.6.3.1 **Adverse Events / Clinical Signs and Symptoms of CS**

- The start and stop date will be imputed to determine if the event is treatment-emergent or not and to derive an imputed AE duration. Imputed AE durations, but not the imputed dates, will be displayed in listings. Imputed AE durations will be flagged in the listings.

Imputation of Event Stop Dates

- If the AE or Clinical Sign/Symptom of CS is not reported as resolved, or is reported as ongoing, or if the status is missing or reported as unknown, a stop date will not be imputed and the duration will not be calculated.
- If the AE or sign/symptom is reported as resolved and:
    i. The stop date is completely missing, the stop date will be imputed as the date of the subsequent visit (i.e. the visit following the AE start date) or study completion date if the subject withdrew prior to a subsequent visit.
    ii. A partial stop date is recorded, and: (1) The stop day is missing and the month is recorded, the stop day will be imputed as the last day of the month; or (2) The stop day is recorded and the month is missing, the stop month will be imputed as the month of the last attended visit; or (3) The stop year is missing; the stop year will be imputed as the year of the last attended visit.
- If the stop date is missing and the event lead to death, the stop date will be imputed as the date of death. The imputed event stop date in that instance will

be displayed in the listings. Any imputed date will be flagged as such in the listings.

Imputation of Event Start Dates

- If the start date is completely missing it will be imputed as the earliest date between the date of the 1st dose and the (imputed) stop date. If the (imputed) stop date occurs before the imputed start date then the (imputed) stop date will be changed to the imputed start date + 1 day.
- If a partial start date is recorded and: (1) The start day is missing and the month is recorded, the start day will be imputed as the first day of the month or the first dose day if the month is the same as the month of the first dose; or (2) The start day is recorded and the month is missing, the start month will be imputed as month of the first dose; or (3) The start year is missing; the start year will be imputed as the year corresponding to the year of the first dose.

5.6.3.2 **Prior, Continuing and New Medications**

They are considered to have started at the earliest relevant date and end at the latest relevant date.

Table 6 displays some examples of date imputation (date format is DD-MMM-YYYY), missing day are listed with "- -" and missing month with "- - -".

Table 6: Example of Partial and Missing Dates Imputation

Data Type	Start Date	Imputed Start Date	First Dose date	Last Dose Date	End Date	Imputed End Date
Prior/Concomitant Meds	--FEB2012	01FEB2012	01JAN2012	01MAR2012	--FEB2012	29FEB2012
Prior/Concomitant Meds	--FEB2012	01FEB2012	15FEB2012	01MAR2012	--MAR2012	31MAR2012
Prior/Concomitant Meds	-----2012	01JAN2012	15FEB2012	01MAR2012	--FEB2012	29FEB2012
Prior/Concomitant Meds	--FEB2012	01FEB2012	15FEB2012	01MAR2012	-----2012	01MAR2012
Adverse Event	--FEB2012	01FEB2012	01JAN2012	01MAR2012	--FEB2012	29FEB2012
Adverse Event	--FEB2012	15FEB2012	15FEB2012	01MAR2012	--MAR2012	31MAR2012
Adverse Event	-----2012	15FEB2012	15FEB2012	01MAR2012	-----2012	16MAR2012£
Adverse Event		15FEB2012	15FEB2012	01MAR2012	--MAR2012	31MAR2012

Data Type	Start Date	Imputed Start Date	First Dose date	Last Dose Date	End Date	Imputed End Date
Adverse Event	--JAN2012	01JAN2012	15FEB2012	01MAR2012		01MAR2012*

£ Subject discontinued on 16MAR2012; * Subject discontinued on 01MAR2012.

5.6.3.3 CS Diagnosis Date

- If the day is missing but both the month and year are non-missing, then the missing day will be imputed the day as 01.
- If both the day and month are missing but the year is non-missing, then the missing day and month will be imputed as 01 January.
- If the date is completely missing, then it will not be imputed.

5.7 *DERIVATION RULES*

5.7.1 Urinary Free Cortisol

When at least four 24-hours urine samples are to be collected to provide a robust estimate of the UFC, as at the final visit of the Maintenance Phase, the mean UFC will be derived from **adequate** 24-hours urine samples only, as follow:

- At least 2 samples must be adequate to derive the mean UFC from the resulting measurements ([3]).
- If only 1 or no adequate 24-hour sample was collected, the mean UFC will not be reported and will be considered missing for both categorization purposes and parametric analytic purposes.

At visits when two 24-hour urine samples were to be collected for calculation of mean UFC:

- If only 1 adequate sample was collected it will be used to represent the mean UFC for that visit.
- If no adequate 24-hour sample was collected, the mean UFC will not be reported and will be considered missing.

An adequate urine sample is defined as an adequate volume collected in 24-hours with an acceptable 24-hour creatinine excretion, i.e. the below criteria should be met to have an adequate sample collection.

- Total volume of urine is at least 400 mL and less than or equal to 4000 mL per day.
- 24-hour Creatinine Excretion (as provided by the central lab) is within the expected ranges or there is a superseding reason for the sample to be outside the expected range (see below for Medical interpretation rules). Table 7 shows the expected ranges used for this study.

Table 7: Minimum 24-hours' Creatinine Excretion to be Considered Adequate

Gender	Age (years)	Minimum 24-hour Creatinine Excretion in Normal Population
Male	18 to 50	18.5 mg/kg/day
	51 to 70	15.7 mg/kg/day
Female	18 to 50	16.5 mg/kg/day
	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.		

Prior to the End of Maintenance Phase database lock and again, prior to the final database lock, the Cmed or Cortendo Medical Monitor will review the urine collection data and determine which samples are not adequate using the following procedure. Using the database freeze data, Cmed will generate a listing of creatinine excretion and urine volume in an xlsx format. The listing (see Listing 16.2.10-1 of the SAP TFL shells) will include subject ID, visit, demographic and safety lab data, and a derived assessment of collection adequacy based strictly upon the volume and 24-hour excretion criteria derived from a normal population (Table 7). The listing will not reveal any restricted data. The Cortendo Medical Monitor will then review the results and indicate (Yes/No) the adequacy of each sample based upon the above criteria for the subject population. The updated xlsx file will be imported in the analysis dataset, and the Medical Review of adequacy will be used to produce the final analysis. A copy of the updated xlsx file will be appended to the classification meeting minutes. A listing of differences between the programmatically derived sample adequacy and the Medical Review derived sample adequacy, by subject, will be generated (see Listing 16.2.10-2 of the SAP TFL shells). A sensitivity analysis of the primary endpoint will make use of the programmatically derived sample adequacy.

5.7.2 Efficacy Endpoints

- **UFC Response (also referred to as Clinical Response for the primary efficacy endpoint):**

The mean UFC will be determined at each visit from adequately collected samples (see Section 6.7.1 for definition of adequately collected samples) and then compared to the ULN.

- UFC response will be met if the mean UFC is ≤ ULN. The subject is considered a responder at a visit based solely on the UFC value (even if there is a dose increase prior to the UFC collection at that visit). However, for purposes of the primary endpoint a subject is considered a responder only if this definition is met at the End of the Maintenance Phase and there is not a preceding dose increase (relative to the Therapeutic Dose) during the Maintenance Phase.
- UFC response will not be met if the mean UFC is > ULN. The subject is considered a non-responder if this definition is met at the End of the Maintenance Phase.

- UFC response will be imputed (as described in Section 6.6.1) if the mean UFC is missing for any reason, if the subject has withdrawn early, if there is a dose increase during the Maintenance Phase (always imputed as non-responder) or if there are not enough adequately collected samples.

- **UFC Improvement:** The UFC will be determined at each visit from adequate samples. UFC improvement is defined as a ≥ 50% reduction from Baseline mean UFC at Months 1, 2, 3, 4, 5, or 6 of the Maintenance Phase. If the UFC and/or Baseline UFC is missing, the UFC improvement will be set to missing. UFC improvements are not categorized accounting for dose increases; however, UFC improvement will be imputed in the same manner as described above for UFC response.
- **Total hirsutism score:** is the sum of all the scores obtained in each of the 9 locations. Total score can vary between 0 and 36. A high score means that the hirsutism is more visible. The total hirsutism score is applicable to females only and will therefore not be derived for males. If one location has a missing score, then the missing score will be imputed as the average of the non-missing scores for that location in the ITT population. If there are more than 25% of the locations (i.e. 3 or more locations out of 9) with a missing location score at a given time point, then the total score will be set to missing.
- **Total peripheral edema score:** is the sum of all the scores obtained in each of the 3 locations. Total score can vary between 0 and 12. A high score means that the edema is more pronounced. If one or more locations has a missing score, then the total score will be set to missing.
- **QoL Questionnaire:** The Cushing QoL questionnaire is a general questionnaire of 12 items that assesses subject health-related quality of life. Answers to QoL are based on Likert scales with five response categories, rated on a scale of 1-5, where '1' corresponds to 'Always' or 'Very much' and '5' to 'Never' or 'Not at all'. Therefore, the lower the score, the lower the health-related quality of life (HRQoL). The total score for QoL is the sum of all the item responses and can range from 12 (worst score) to 60 points (best score). A standardized total score on a scale from 0 (worst HRQoL) to 100 (best HRQoL) will be calculated with the following formula:

Standardized total score = $\frac{TotalScore - \min}{\max - \min} \times 100$

where 'min' is the minimum (min=12 if all 12 item responses are non-missing), and 'max' is the maximum possible score (max=60 if all 12 item responses are non-missing).

If more than 3 items have a missing response, then the total score will be considered missing for that visit. The score can be interpreted (as above) if the number of unanswered items does not exceed 3 (25% of the questions). In this case, the standardized total score will have min = the number of item responses that are non-missing and max = 5 x the number of items responses that are non-missing.

- **Beck Depression Inventory II:** This questionnaire comprises 21 questions with a score from 0 to 3. Scores for each question are summed to create an overall score. A score between 0 and 13 indicates minimal depression, 14 to 19 mild depression, 20 to 28

moderate depression and 29 to 63 severe depression. Scoring information for the 21 questions is in Appendix 15.4. If one question has a missing score, then the missing score will be imputed as the average of the non-missing scores for that question in the ITT population. If there are more than 25% of the locations (i.e. 6 or more questions out of 21) with a missing score at a given time point, then the total score will be set to missing.

- **Acne Visual Analog (VAS) Questionnaire:** Each type of lesion is graded with a value depending on the severity: 0 - No Lesions, 1 - Greater than or equal to one comedone, 2 - Greater than or equal to one papule, 3 - Greater than or equal to one pustule, 4 - Greater than or equal to one nodule. Factor is dependent on the location of the lesion: 2 – Forehead, 2- Right Cheek, 2- Left Cheek, 1 – Nose, 1 – Chin and 3- Chest and Upper Back.

The score for each area (Local score) is calculated using the formula:

Local score = Factor × Grade (0-4)

The global score is the sum of local scores as follows:

Global score = Sum (all local scores)

If one area has a missing local score, then the missing local score will be imputed as the average of the non-missing local scores for that area in the ITT population. If there are more than 25% of the areas (i.e. 2 or more areas out of 6) with a missing local score at a given time point, then the global score will be set to missing.

- **Clinical Benefit:** a subject with Clinical Benefit meeting all 4 criteria at any visit after completing Dose Titration (M1 and higher) as listed below:
    1. Mean UFC ≤ ULN, and
    2. No COR-003 dose increase relative to the Therapeutic Dose (prior to the nominal visit in the Maintenance Phase only), and
    3. A clinically meaningful improvement in any one Baseline CS comorbidity (diabetes, hypertension, hypercholesterolemia, weight) without confounding medication change, as described in the "Clinically meaningful improvement" bullet point later in this section, and
    4. No study drug-related (i.e. probable or definitely related as per the Investigator) TEAE classified as severe or worse.
- **Clinical Benefit regardless of dose increase:** a subject with Clinical Benefit meeting all 3 criteria listed below (see above description of Clinical Benefit for further details):
    1. UFC response as indicated by UFC ≤ ULN, and
    2. A clinically meaningful improvement in any one Baseline CS comorbidity (diabetes, hypertension, hypercholesterolemia, weight) without confounding medication change as described below, and
    3. No study drug-related TEAE classified as severe or worse.
- **Clinical Benefit with Partial UFC Normalization (i.e., UFC Improvement):** a subject with partial Clinical Benefit meeting all 3 criteria listed below (see above description of Clinical Benefit for further details):
    1. UFC improvement as indicated by a ≥ 50% reduction from Baseline, and

2. A clinically meaningful improvement in any one Baseline CS comorbidity (diabetes, hypertension, hypercholesterolemia, weight) as described below but regardless of medication change, and
3. No study drug related TEAE classified as severe or worse.

- **Clinically meaningful improvement:** a subject with clinical meaningful improvement in a comorbidity is one who meets at least one of the criteria listed below:
    1. Fasting glucose: relative decrease of at least 17.9% from Baseline and Baseline result above normal range AND also maintained stable doses of background anti-diabetic medications OR reduced the dose of background anti-diabetic medications OR permanently discontinued anti-diabetic medications OR if not treated with anti-diabetic medications at Baseline, not started on anti-diabetic medication at or prior to the nominal visit.
    2. Hb1Ac: an absolute decrease of 0.3 percentage units from Baseline and Baseline result outside of normal range AND also; maintained stable doses of background anti-diabetic medications OR reduced the dose of background anti-diabetic medications OR permanently discontinued anti-diabetic medications OR if not treated with anti-diabetic medications at Baseline, not started on anti-diabetic medication at or prior to the nominal visit.
    3. SBP, DBP: an absolute decrease of 2 mmHg in either SBP or DBP among subjects with hypertension AND also; maintained stable doses of background antihypertensive medications OR reduced the dose of background antihypertensive medications OR permanently discontinued antihypertensive medications OR if not treated with antihypertensive medication at Baseline, not started on antihypertensive medication at or prior to the nominal visit.
    4. LDL-C: a relative 24% decrease in LDL-C from Baseline and **without** a corresponding relative decrease in HDL-C of greater than 12%, where Baseline LDL-cholesterol result is outside of the normal range AND also; maintained stable doses of background cholesterol-lowering medications OR reduced dose of background cholesterol-lowering medications OR permanently discontinued use of cholesterol-lowering medications OR if not treated with cholesterol-lowering medication at Baseline, not started on cholesterol-lowering medication at or prior to the nominal visit.
    5. Body weight: a relative decrease of at least 5% from Baseline, without addition of weight loss medication at or prior to the nominal visit.

5.7.3 Vital Signs and Abdominal Girth

- **Blood Pressure and Abdominal Girth**: are collected in triplicate at each visit. The mean of the assessments will be calculated if there are at least two assessments and used in the summary tables.

5.7.4 Study Day

- **Study Day:** is calculated using the start date of assessment, blood draw or specimen collection. Study day is derived from the date of first dose of study drug intake for the Dose Titration Phase:
    1. If date of assessment is before the date of first dose: Study Day = [Start Date of Assessment – Date of First Dose of Study Drug],
    2. If date of assessment is after the date of first dose: Study Day = [Start Date of Assessment – Date of First Dose of Study Drug + 1],
    3. If date of assessment is the same as the date of first dose: Study Day = 1,
    4. If the first dose was never given the study day will be missing.

6 Analysis Sets

The following populations will be considered in the data analysis:

All Subjects

This population is used for all data listings and selected data summaries. This includes all subjects enrolled into the study, defined as having signed an informed-consent form, regardless of whether or not they received the study drug. Subjects who did not receive study drug were considered screen failures; screen failures are summarized only in the summaries of subject disposition and analysis population.

Intent-to-Treat (ITT) Population

The ITT population will include all subjects who receive at least one dose of COR-003. The ITT is the primary population and will be used for the evaluation of efficacy and all safety analyses. Subjects will be summarized as follows for by-visit tabulations:

- For the Dose Titration Phase, subjects will be summarized under the different doses they received during that period (see Section 6.2).
- For the Maintenance Phase, subjects will be summarized based on their Therapeutic Dose (i.e. the dose they received on the date they entered the Maintenance Phase), regardless of any dose changes.
- For the Extended Evaluation Phase, subjects will be summarized under the most recent dose level received.

For the Baseline characteristics and demographics, AEs (including Clinical Signs and Symptoms of CS) and Medications, summaries by dose group will be based on the Therapeutic Dose.

Dose Titration (DT) Population

The DT population will consist of all ITT subjects who entered the Dose Titration Phase but did not start the Maintenance Phase. This population, which is not pre-specified in the protocol, will be used for supportive evaluations of Baseline characteristics, selected efficacy, adverse events and safety laboratory outputs.

Maintenance (M) Population

The M population will consist of all ITT subjects who entered the Maintenance Phase and completed visit M1 (D1). This population will be used for supportive evaluations of Baseline characteristics and the primary and selected other efficacy endpoints during the Maintenance Phase.

Maintenance-Completer (MC) Population

The MC population will consist of all ITT subjects who entered the Maintenance Phase and completed the End of Maintenance Phase (Month 6 [Day 180]) visit. This population, which is not pre-specified in the protocol, will be used for supportive evaluations of Baseline characteristics, study drug exposure and compliance, the primary efficacy endoint, all secondary efficacy endpoints and ACTH during the Maintenance Phase.

Per Protocol (PP) Population

The PP population will consist of all ITT subjects who entered and completed the Maintenance Phase of the study and had no major protocol deviations that may affect the primary efficacy assessment (see Section 8.1). This population will be used for supportive evaluations of study drug exposure and compliance, the primary efficacy endpoint and the secondary endpoints of UFC response and/or improvement rates by visit during the Maintenance Phase.

Pharmacokinetic (PK) population

The PK population may include all ITT subjects with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement. The definitive description of the PK population will be provided in a separate population PK/PD analysis plan.

Pharmacodynamic (PD) population

The PD population may include all ITT subjects with at least one adequately collected 24-hour urine sample for UFC. The definitive description of the PD population will be provided in a separate population PK/PD analysis plan.

Table 8 below describes which analysis population will be used for the different analyses considered in this SAP. Detailed information regarding each analysis and the analysis populations used is given in Section 8.

Table 8: Analysis populations broken down by analysis type

Analysis Type	Population							
	All	ITT	DT	M	MC	PP	PK	PD
Summary of Subject Disposition	X	X						
Summary of Analysis Populations	X							
Summary of Demographics and Baseline Characteristics		X	X	X	X	X		
Summary of Protocol Deviations Leading to Exclusion from the PP Population		X						
Summary of Medical History		X	X		X			
Summary of Disease Characteristics		X	X		X			
Summaries of Prior, New and Continuing Medications		X						
Summaries of Prior CS Drug Therapy, Radiotherapy and Surgery		X						
Study Drug Exposure and Compliance		X			X	X		
Primary Analysis of UFC Response (ie, Clinical Response after 6 Months of Maintenance Treatment)		X		X	X	X		
Other Analyses of UFC Response and/or Improvement		X		X	X	X		
Summaries and plots of UFC Response and/or Improvement by Visit (and/or Dose, if applicable)		X	X*	X*	X	X*		
Summaries of UFC values by Visit (and/or Dose, if applicable)		X			X			
Individual Plots of Change from Baseline to End of Maintenance Phase in UFC					X			

Analysis Type	Population							
	All	ITT	DT	M	MC	PP	PK	PD
Plots of Effect of Dose Increases During the Maintenance Phase of UFC					X			
Summaries of Serum and LNSC		X			X			
Summaries and Plots of LNSC Normalisation		X			X			
Summaries and plots of CS Comorbidities Biomarkers		X			X			
Analyses of Change from Baseline in CS Comorbidities Biomarkers		X			X			
Summaries and plots of Clinical Signs and Symptoms of CS		X			X			
Summaries of Cushing QoL Total Score		X			X			
Summaries of Total BDI-II Score		X			X			
Summaries of OGTT and Spot Albumin/Creatinine Ratio		X			X			
Summaries of Clinical Benefit Rate		X						
Summaries of changes to Antihypertensive, Anti-diabetic, Cholesterol-lowering Medications		X						
Shift Tables of Visible Signs of Hypercortisolism from Photograph Scores		X						
Summaries of within Visit Variability for Applicable Efficacy Parameters		X						
Summaries of Diabetes Mellitus, Hypertensiion, Hypercholesterolaemia and Obesity Responders		X						
Summaries of AEs		X	X^					

Analysis Type	Population							
	All	ITT	DT	M	MC	PP	PK	PD
Summary Statistics and Box-and-whisker plots of Absolute Clinical Laboratory Results		X	X^					
Summaries of Change from Baseline in Clinical Laboratory Assessments		X						
Shift Tables and all other Plots of Clinical Laboratory Assessments		X	X^					
Summaries of Abnormal Spot Albumin to Creatinine Ratio		X						
Summaries of Hormones and Biomarkers Laboratory Evaluations		X						
Summaries of ACTH		X	X		X			
Summaries and Plots of Vital Signs		X						
Summaries and Plots of ECG Parameters		X	X^					
Summaries of Tumor Size and Tumor Volume		X						
Data listings	X							

* Selected summaries only, see Section 8.8 for further details

^ Selected Summaries only, see Section 8.11 for further details.

Note: There are no entries under the PK and PD columns, since the population PK and PD endpoints and planned analyses will be described in a separate population PK/PD analysis plan.

7 Methods of Analyses and Presentations

7.1 *PROTOCOL DEVIATIONS*

Protocol deviations are departures from the protocol. Protocol deviations may be identified from different sources and methods such as algorithmic queries or medical reviews of the clinical database, Clinical Research Associate (CRA) monitoring notes, audits, etc.

Protocol deviation criteria are defined and documented separately from this SAP in the protocol deviation criteria form (PDCF). Protocol deviations that should lead to exclusion from one or more of the analysis populations, including the PP population, are also indicated in the PDCF.

Protocol deviations thus identified will be manually reviewed during a classification meeting that will be held prior to the Maintenance Phase database lock. The PP population will be finalized following this meeting. Protocol deviations leading to exclusion from the PP population will be termed as major protocol violations and summarized by dose group and for All dose groups combined. A second classification meeting will be held prior to the Extended Evaluation Phase database lock, but none of the protocol deviations during this Phase will lead to exclusion from the PP population.

All subjects with protocol deviations impacting the Clinical Study Report and/or data integrity will be listed, including protocol deviations leading to exclusion from the PP population.

7.2 *DEMOGRAPHIC AND BASELINE CHARACTERISTICS*

Demographic and Baseline characteristics (age, sex, race, ethnicity, height, weight, BMI, child bearing potential if female (Yes [Y]/No [N]), work night shift or alternate work/sleep schedule (Y/N), diagnosis of CD (Y/N), diagnosis of diabetes (Y/N), diagnosis of impaired fasting glucose without diabetes (Y/N), diagnosis of hypertension (Y/N)) will be summarized for all subjects in the ITT, DT, M, MC and PP populations, and the summary will be performed by dose group and for All dose groups combined.

Diagnosis of CD, diagnosis of diabetes, and diagnosis of hypertension will be based on the presence (Y/N) of the condition as recorded in the Diagnosis and History of CS eCRF. Diagnosis of impaired fasting glucose without diabetes (i.e., prediabetes) will be based on the response (Y/N) to the question “Is subject pre-diabetic?” in the OGTT eCRF at Baseline.

7.3 *MEDICAL HISTORY AND DISEASE CHARACTERISTICS*

Medical history and disease characteristics will be summarized for all subjects in the ITT, DT and MC populations by dose group and for All dose groups combined.

Medical history, CS history, CS diagnosis and associated laboratory values as well as CS prior medical treatments, prior radiotherapies and prior surgeries will be listed for all subjects.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), the version provided in the corresponding table and listing footnotes, and tabulated by System Organ Class and Preferred Term.

The following disease characteristics will be summarized:

- Disease etiology: CD, Adrenal-dependent CS (includes adenomas and hyperplasia), Ectopic ACTH secretion, Ectopic corticotropin-releasing hormone [CRH] secretion, Etiology unknown,
- Time since CS diagnosis (months) (calculated relative to the date of first dose of COR-003).
- Associated Metabolic Complications: Diabetes mellitus, hypertension, hypercholesterolemia, osteoporosis, and reproductive dysfunction), Others,
- Duration of associated medical complications,
- Receiving medication (Yes, No) for associated medical complications,
- Prior medication (Yes, No) for management of CS,
- Prior radiotherapy (Yes , No) for management of CS (pituitary, adrenal other),
- Prior surgery (Yes, No) for management of CS,
- Locations of prior radiotherapies (pituitary, adrenal, other) for management of CS,
- Number of prior surgeries (1, 2, 3 and > 3) for management of CS,
- Treatment naive (Yes, No) for management of CS (treatment naive means the subject has not received either prior medication or prior radiotherapy and has not had surgery),
- Baseline Mean UFC from adequate 24-hour urine samples.

7.4 *SUBJECT DISPOSITION*

A summary of subject disposition will be presented, showing the number and percentage of subjects treated, as well as the number and percentage of subjects who completed each study phase or withdrew from the study for the ITT population, alongside the primary reason for discontinuation. For the Dose Titration Phase, the subjects treated will be counted in two ways - under any dose they received and under the last dose they received (i.e. two rows of treated subjects will be displayed in the summary). The summary will be presented for all subjects, by the last dose level at the time of discontinuation or completion for the Dose Titration Phase and Extension Evaluation Phase (see Section 6.2), and by dose group for the Maintenance Phase. Information on analysis populations, study phase completion and discontinuation will also be displayed in subject listings.

For the primary reason for discontinuation, the reasons “Adverse event”, “QTcF interval prolongation” and “Liver function test” will be combined in the disposition table into a single category of “Adverse event”.

Completion/ongoing/discontinuation status from each phase will be derived from the Treatment Completion Phase eCRF. A subject listing will be provided and will include the protocol amendment under which the subject was enrolled.

7.5 *PRIOR AND CONCOMITANT MEDICATIONS*

Medications will be coded using the WHO-DRUG dictionary; the version will be provided in the corresponding table and listing footnotes. The medications, depending on when they started and stopped relative to the date of first dose of COR-003, will be classified in the following categories:

- Prior Medication: Any medication that stopped before the date of the first dose of study drug.
- Continuing Medication: Any medication that started before the date of the first dose of study drug and stopped on or is ongoing after the date of the first dose of study drug.
- New Medication: Any medication that started on or after the date of the first dose of study drug.
- New medications and continuing medications will be classified further by when they were used relative to each study phase.
- Continuing Medication by phase: Any medication that started before the date of the first visit of each study phase, and stopped on or is ongoing after the date of the first visit of the study phase.
- New Medication by phase: Any medication that started on or after the date of the first visit of the study phase and before the first visit of the next phase.

Note: In case of partial or missing start and stop dates, imputation examples and rules detailed in Table 6 and Section 6.6.3 will be used.

All summaries below will be presented for the ITT population.

All medications (including, separately for each, medications for management of CS, anti-diabetic medications, antihypertensive medications and cholesterol-lowering medications) will be summarized, at a minimum, by therapeutic class and by study phase. Listings will be generated that also include preferred terms.

New medications summaries will be presented by study phase. New medications started during the Dose Titration or the Extended Evaluation Phase will be summarized under the most recent dose level received. New medications started during the Maintenance Phase will be summarized at the Therapeutic Dose. New medications will only be counted in the phase when the medication was started, e.g. if a new medication is started in the Dose Titration Phase and continued into the Maintenance Phase it is only counted under the Dose Titration Phase.

For summaries of prior and continuing medications for the ITT population across all 3 phases combined, summaries by COR-003 dose level will use the dose level received during the Maintenance Phase (ie, the Therapeutic Dose). Subjects in the ITT population who did not reach

the Maintenance Phase will be summarized under the last COR-003 dose level received in the Dose Titration Phase.

A medication will be counted only once under a therapeutic class, and where applicable, only once under a preferred term within a therapeutic class.

Separate subject data listings will be provided for the following categories. In addition, prior, continuing and new medications will be flagged within each listing.

- Medications used for the management of CS,
- Anti-diabetic medications,
- Antihypertensive medications,
- Cholesterol-lowering medications,
- Other medications

7.6 *PRIOR CUSHING'S SYNDROME THERAPY*

Prior CS therapies will be summarized for the ITT population. All summaries will be prepared for each dose group and for All dose groups combined.

7.6.1 Prior Cushing's Syndrome Drug Therapy

A summary of the prior medications used for management of CS will be provided by therapeutic class, preferred term and for each dose group and for All dose groups combined (See Section 8.5).

The total estimated duration of each preferred term will be calculated as the number of unique days the drug was taken. (e.g. each unique period of drug use will be counted, any overlapping periods will be counted only once). The total estimated duration will be summarized by dose group and for All dose groups combined.

Under each CS drug therapy preferred term, the number and percent of subjects taking each dose of CS drug therapy at the time of enrollment will be presented. For dose categories within a preferred term, the total estimated duration as defined above will be listed.

7.6.2 Prior Radiotherapy for Cushing's Syndrome

The number and percent of subjects who received prior radiotherapy for CS will be summarized. Summaries will be presented for the following:

- Location (pituary, adrenal gland, other).
- Time since end of radiotherapy (date of first dose of COR-003 - end of radiotherapy date).
- Duration of radiotherapy (end of radiotherapy date – start of radiotherapy date +1).
- Cumulative dose.

All radiotherapy data (including type and outcome) will be listed.

7.6.3 Prior Surgery for Cushing's Syndrome

The number and percent of subjects who received prior surgery for CS and the procedure they received will be presented. The estimated time since surgery data will be summarized by location of surgery, surgical procedure and overall.

7.7 STUDY DRUG EXPOSURE AND/OR COMPLIANCE

Days on study drug, study drug compliance and average daily dose will be summarized by study phase (Dose Titration Phase, Maintenance Phase and Extended Evaluation Phase), by visit (for the Maintenance and Extended Evaluation Phases), by dose group and for All dose groups combined for the ITT, MC, and PP Populations. The cumulative dose will also be summarized for the Maintenance and Extended Evaluation Phases only.

For the Dose Titration Phase and the Extended Evaluation Phase, subjects will be summarized under each dose level they received, and for a given dose level only data related to that dose will be taken into account to derive the days on study drug, study drug compliance and average daily dose for both phases and cumulative dose for the Extended Evaluation Phase.

The occurrence and timing of dose interruptions, dose reductions and dose increases will be listed, and the incidence of subjects with dose unchanged, decreased and increased between visits will be summarized by study phase (for the Maintenance and Extended Evaluation Phases only), by dose group and for All dose groups combined.

7.7.1 Study Drug Exposure

The overall days on study drug by study phase is defined as the number of days between the first dose given at the start of the phase and the last dose taken at the end of the phase + 1 day. The following convention will be used:

- Start of Dose Titration Phase: date of first dose
- End of Dose Titration Phase: last dose date (for subjects who discontinued before the Maintenance Phase) or date of drug returned at M1 (D1) visit.
- Start of the Maintenance Phase: date of drug dispensed for M1 (D1) visit
- End of the Maintenance Phase: last dose date on study completion page for Maintenance Phase
- Start of Extended Evaluation Phase: last dose date on study completion page for Maintenance Phase
- End of Extended Evaluation Phase: last dose date on study completion page for Extended Evaluation Phase.

The days on study drug in each visit i in the Maintenance and Extended Evaluation Phases is defined as the number of days between the date the study drug was returned at visit i+1 and the date the study drug was dispensed at visit i, + 1 day. If a subject discontinued at visit i+1, then the last dose date of study drug will be used rather than the date the study drug was returned.

Subjects who do not return the study drug at visit i+1 will not included in the summaries for visit i.

In addition overall study drug exposure acoss the entire study will be calculated and summarized for all subjects combined (i.e. regardless of dose) as the time between first dose and last dose + 1 day, regardless of the study phase. The overall study drug exposure for the combined Maintenance and Extended Evaluation Phases will be calculated and summarized by Therapeutic Dose.

7.7.2 Compliance

Compliance by subject is calculated in a visit (or study phase) as follows:

$$\text{Compliance}(\%) = \left(\frac{\text{Cumulative dose received (mg)}}{\text{Cumulative dose expected (mg)}} \right) \times 100$$

For any dose level the cumulative expected dose for visit i is calculated as the following:

$$\text{Cumulative dose expected (mg)}_i = \left((\text{DL} + 1) \times 150\right) \times \left(\text{Date tablets returned}_{i+1} - \text{Date tablets dispensed}_i + 1\right)$$

Where DL is the numeric dose level for the treatment period.

For visits during the Maintenance Phase, DL is the planned dose level at the beginning of the Maintenance Phase.

The cumulative dose received for visit i is the calculated as the following:

$$\text{Cumulative dose received (mg)}_i = \left(\text{Number of tables dispensed}_i - \text{Number of tablets returned}_{i+1} + \text{Number of tablets lost}_{i+1}\right) \times 150$$

For a study phase, the cumulative dose received is the sum of the cumulative dose received for all the visits within the given study phase. Similarly the cumulative dose expected for a study phase is the sum of the cumulative dose expected for all the visits within the given study phase.

The following rules will be applied when determining the compliance:

- If the number of tablets returned is missing at a visit i+1, then the reconciliation will be done at the next visit when the number of tablets returned is available. In such a case, the compliance at visit i cannot be calculated, however.
- If the number of tablets returned is never available, the compliance will not be calculated.
- If the number of tablets lost is missing it will be assumed to be 0.

Compliance will be summarized using descriptive statistics, and the number (%) of subjects with compliance < 80 %, between 80% and 120% and > 120% will also be reported by study phase and dose level.

For the Dose Titration Phase compliance will be summarized under the relative dose, compliance for the entire Dose Titration Phase will be summarized under All dose groups.

For the Maintenance Phase compliance will be summarized by visit and overall under the dose level received at the beginning of the Maintenance Phase.

For the Extended Evaluation Phase compliance will be summarized by visit under the relative dose group. The overall compliance during the Extended Evaluation Phase will be summarized under All dose groups.

7.7.3 Average Daily Dose

The average daily dose for each study phase, dose level and visit (for the Maintenance and Extended Evaluation Phases only) will be derived as the cumulative dose received divided by the number of days on study drug for the considered period. Also, the average daily dose level will be calculated across all doses for each phase and for the entire study duration.

If the dose level changes between visits during the Dose Titration Phase or the Extended Evaluation Phase, the average daily dose will be assigned to more than one dose level for the interval as follows: the sum of the cumulative dose received during the visit interval will be divided by the number of days in the visit interval on study drug at each dose level. For the Maintenance Phase, the average daily dose will only be summarized under the dose level assigned at the beginning of the phase.

7.8 *EFFICACY DATA ENDPOINTS AND ANALYSES*

7.8.1 Primary Efficacy Endpoint and Analyses

For the primary efficacy analysis, UFC response to COR-003 is defined as a reduction in mean 24-hour UFC levels to ≤ ULN following 6 months of Maintenance Phase therapy without dose increase.

Analysis Method

The proportion of responders at the End of Maintenance Phase visit, following 6 months of treatment in the Maintenance Phase, for All dose groups combined will be estimated using a generalized linear model with repeated measurements and with region (US vs. non-US), concurrent CS medical conditions (diabetes [Yes/No], hypertension [Yes/No]), age (rounded median split based on the ITT population), sex, disease duration (years), prior CS medication (Yes/No), prior radiation therapy (Yes/No) as Baseline covariates and visit as an independent factor. Prior CS medication and prior radiation therapy will be based on the response (Y/N) as recorded in the Diagnosis and History of CS eCRF. Region (US vs. non-US) was not a pre-specified

effect in the longitudinal models that were pre-specified in the protocol, but it has been added to the model to adjust for possible regional differences in efficacy. All repeated measurement models that will be utilized to analyze the primary and secondary efficacy endpoints will include visits from the Maintenance Phase only (i.e. from M1 [D1] (if applicable) or M1 [D30] to M6 [D180] only).

The least squares mean (LSMEAN) estimate of the UFC response after 6 months of treatment in the Maintenance Phase alongside its 95% Wald CI will be presented as well as the associated standard error. P-values for each parameter of the model from the Type III tests of fixed effects will also be presented. Only assessments performed during the Maintenance Phase (excluding all follow-up assessments) will be included in the analysis as per the rules described in Section 6.1 (visit window).

Estimation will be performed based on a generalized linear model with repeated measurements with a logit link using SAS® PROC GLIMMIX with LSMEANS. The ILINK option will be used to obtain the estimated proportions. An unstructured covariance matrix will be selected for the repeated measure covariance. For any repeated measurements model utilized in an analysis, if the unstructured covariance matrix results in non-convergence of the model, other covariance structures will be explored by use of Akaike's information criteria. If the model still does not converge, the model will be simplified by keeping only the covariates/effects that have Type III tests of fixed effects p-values ≤ 0.35.

Primary analysis

The primary analysis will be based on the ITT population. As described in Section 6.5, subjects who: a) withdrew prior to the end of the Maintenance Phase, including those in the DT population, or b) have a dose increase (relative to their Therapeutic Dose) during the Maintenance Phase or c) previously received radiation therapy and exhibited no rebound increase in mean UFC following withdrawal of COR-003 immediately after the end of the Maintenance Phase will be imputed as non-responders. Subjects in the DT population will be considered as non-responders at each visit (i.e. from M1 [D30] to M6 [D180]) in the Maintenance Phase. Subjects who entered the Maintenance Phase but withdrew prior to the End of the Maintenance Phase will be considered as non-responders at each visit in the Maintenance Phase after their withdrawal. Subjects with a dose increase (relative to their Therapeutic Dose) during the Maintenance Phase will be considered as non-responders at each visit in the Maintenance Phase after the dose increase. Subjects who previously received radiation therapy and exhibited no rebound increase in mean UFC following mean UFC following withdrawal of COR-003 immediately after the end of the Maintenance Phase will be considered as non-responders at M6 [D180] only. All other subjects who have missing mean UFC at M6 [D180] for any other reason, including insufficient number of adequate samples, will also be considered non-responders at M6 [D180].

A supportive analysis that does not require statistical modeling will also be performed by calculating a Clopper-Pearson two-sided 95% CI for the one-sample binomial proportion.

The analysis of the primary efficacy endpoint will also be performed on the M, MC, and PP populations.

Sensitivity analyses for primary analysis

Three supportive analyses will be run using the first, second and third imputation methods described in Section 6.6.1. Analyses results from the M and MC populations with each of the three imputation schemes will also be presented to support the primary analysis conclusions.
In addition, to assess the impact of the protocol deviations on the study results, the same analysis will be repeated on the PP population using each of the three imputation schemes.

P-values for each parameter of the model from the Type III tests of fixed effects will also be presented. Only assessments flagged for analysis, collected at a nominal visit (see Section 6.3) during the Maintenance Phase (excluding follow-up assessments) will be included in the analysis.

A supportive analysis that does not require statistical modeling will also be performed by calculating a Clopper-Pearson two-sided 95% CI for the one-sample binomial proportion.

7.8.2 Secondary Efficacy Endpoints and Analyses

All secondary efficacy endpoints are assessments of outcomes during the Maintenance Phase of the study. In general, however, descriptive summaries will also be presented in the Dose Titration Phase across All Visits by dose group and All dose groups combined for endpoints that were also planned to be assessed during the Dose Titration Phase. In descriptions of some of the graphical presentations, however, it will be stated that the graphs will be produced not just for the Maintenance Phase but for the Extended Evaluation Phase as well.

7.8.2.1 CS Comorbidities Biomarkers

Eight CS comorbidities biomarkers (fasting glucose, HbA1c, SBP, DBP, total cholesterol, LDL-C, HDL-C, body weight) are identified in Section 4.2. In addition, CRP, BMI and abdominal girth are also considered as CS comorbidities biomarkers. It should be noted that change from Baseline in CRP during the Maintenance Phase is already identified as a secondary efficacy endpoint in Section 4.2.

The data for the 11 CS comorbidities biomarkers will be summarized and analyzed for the ITT population and, where specified in Table 8, the MC population.

The statistical model for the End of Maintenance Phase will include only the visits during the Maintenance Phase. For HbA1c and abdominal girth, the scheduled visits in the Maintenance Phase are M1 [D1], M3 [D90], and M6 [D180]. For all other CS comorbidities biomarkers, the scheduled visits are all the visits in the Maintenance Phase listed in Table 5. No imputation for missing data beyond that embedded within the analysis method (repeated measures model) will be made. To account for the multiplicity of statistical tests on the CS comorbidities biomarkers primary endpoints, a Hochberg method will be applied for the adjustment of the statistical

significance level for the 8 CS comorbidities biomarkers that were pre-specified in the protocol (see further details in Section 6.5).

For each of the 11 CS comorbidities biomarkers (fasting glucose, HbA1c, SBP, DBP, total cholesterol, LDL-C, HDL-C, body weight, abdominal girth, CRP and BMI), the following summaries, analyses and graphics will be provided. All data will be presented in subject listings.

Statistical Summaries and Univariate Tests

The CS comorbidities biomarkers results, including baseline, change from Baseline and percentage change from Baseline will be summarized by study phase, visit and/or dose group and for All dose groups combined.

Wilcoxon signed rank tests comparing the Baseline results to each post-baseline visit will be performed by dose group and for All dose groups combined. The median difference between Baseline and post-baseline results and its associated distribution-free 99% CI, using the Hahn and Meeker method [5], and two-sided p-value from the Wilcoxon signed rank test will be displayed. The Wilcoxon signed rank tests will be performed and the 99% CIs will be obtained using SAS® PROC UNIVARIATE. The results of these tests are for descriptive purposes only and are supportive to the results from the first longitudinal analysis described below. In general, due to the small sample sizes, results by dose group from univariate tests may not show nominal significance.

Longitudinal Analyses

Changes and percent changes from Baseline will be presented for the Maintenance Phase in All dose groups combined and will each be estimated using a generalized linear model with repeated measurements for nominal visit (M1 [D30] to M6 [D180]) and with region (US vs. non-US), concurrent CS medical conditions (diabetes [Yes/No], hypertension [Yes/No]), age (rounded median split), sex, disease duration (years), prior CS therapy (Yes/No), prior radiation therapy (Yes/No) and the corresponding Baseline CS comorbidity biomarker result as Baseline covariates, visit as an independent factor, and subject as a random effect. The Baseline CS comorbidity biomarker result was not a pre-specified covariate in the model described in the protocol, but it has been included in the model to adjust for the possible effect of the Baseline values on the magnitudes of the changes from Baseline.

Estimation will be performed using SAS® PROC MIXED with LSMEANS and REPEATED statement. An unstructured covariance matrix will be selected for the repeated measure analysis.

The LSMEAN estimate of the change from Baseline in each CS comorbidities biomarker at each post-baseline visit alongside its two-sided 99% CI will be presented with the associated standard error and two-sided p-value. The p-values corresponding to the End of the Maintenance Phase visit (Month 6 [Day 180]) will be assessed for statistical significance using the Hochberg method at a family-wise error rate of 0.05. The 99% CIs are considered as supportive results.

Two-sided p-values for each parameter of the model from the Type III tests of fixed effects will also be presented.

A separate longitudinal model for the changes from Baseline will be provided with the time trend p-value presented. The results from this separate longitudinal model will be supportive to the results from the first longitudinal model described above. The change from Baseline in All dose groups combined will be estimated using a generalized linear model with repeated measurement (study day [from date of first dose]) and with region (US vs. non-US), concurrent CS medical conditions (diabetes [Yes/No], hypertension [Yes/No]), age (rounded median split), sex, disease duration (years), prior CS therapy (Yes/No), prior radiation therapy (Yes/No), Baseline CS comorbidity biomarker result as Baseline covariates, study day as an independent factor, and subject as a random effect.

Estimation will be performed using SAS® PROC MIXED with LSMEANS and REPEATED statement. An unstructured covariance matrix will be selected for the repeated measure analysis.

P-values for each parameter of the model from the Type III tests of fixed effects will also be presented. All assessments (including unscheduled / repeat assessments) performed during the Maintenance Phase (excluding follow-up assessments) will be included in the analysis.

Incidence of Abnormal Values and Shifts from Baseline

Incidence of abnormal results (i.e. outside of the normal range) for fasting glucose, HbA1c, total cholesterol, LDL-C, HDL-C, and CRP will be summarized for each study phase by visit and by dose group and for All dose groups combined.

Shifts from Baseline from the normal range (Low, Normal, High and abnormal [low/high]) for fasting glucose, HbA1c, total cholesterol, LDL-C, HDL-C, and CRP will be summarized for each study phase (Maintenance and Extended Evaluation Phases) by dose group and visit.

Additional Summaries

The absolute mean and median and the mean and median change from Baseline of the blood pressure assessment at Month 6 (or the last assessed visit in the Maintenance Phase) will be presented in the M population both overall and broken down by diagnosis of hypertension at baseline (Yes/No) and use of blood pressure medication at any time between the first dose of COR-003 in the study and the End of the Maintenance Phase (Yes/No). Distribution-free 99% CIs of the median change from Baseline will be generated using SAS® PROC UNIVARIATE.

Shifts in hypertensive status between Baseline and Month 6 (or the last assessed visit in the Maintenance Phase) will be presented for All dose groups combined in the M population. The hypertensive status will be derived as Normal, pre-hypertension, hypertension stage 1 or hypertension stage 2 as defined in the protocol appendix I.

Shifts in subject diabetes status between Baseline and Month 6 (or the last assessed visit in the Maintenance Phase) will be presented for All dose groups combined in the M population. The diabetes status will be derived as Normal, pre-diabetes or diabetes as defined in the protocol appendix H.

Shifts in subject HbA1c category between Baseline and Month 6 (or the last assessed visit in the Maintenance Phase) will be presented for All dose groups combined in the M population. The HbA1c categories are defined as <5.7%, 5.7 – <6.5%, 6.5 – <8.0% and ≥8.0%.

Similar shifts in subject status or category between Baseline and Month 6 (or the last assessed visit in the Maintenance Phase) with respect to each of the other CS comorbidity biomarkers will also be presented for All dose groups combined in the M population. The fasting glucose categories are < 6.1, 6.1 – 6.9, and >6.9 mmol/L. The total cholesterol categories are < 200, 200-239, and ≥240 mg/dL. (Note: 200 mg/dL=5.172 mmol/L; 240 mg/dL=6206 mmol/L.) The LDL-C categories are <70, 70 - <100, 100 - <130, and ≥130 mg/dL. (Note: 70 mg/dL=1.8102 mmol/L; 100 mg/dL=2.586 mmol/L; 130 mg/dL=3.3618 mmol/L) The HDL-C categories are <40, 40 - <60, and ≥60 mg/dL. (Note: 40 mg/dL=1.034 mmol/L; 60 mg/dL=1.552 mmol/L) The BMI categories are <18.5, 18.5 - <25, 25 - <30, 30 - <40, and ≥40 kg/m^2. The abdominal girth categories for males are ≤102 and >102 cm, and for females ≤88 and >88 cm.

Graphical Representation

For All dose groups combined, the LSMEAN of the change from Baseline for each parameter at each visit in the Maintenance Phase alongside its 99% CI will be plotted.

The percentage of subjects using antihypertensive, anti-diabetic and cholesterol-lowering drugs prior to the first dose (i.e., Baseline) and at the end of Maintenance Phase will be presented by Maintenance Phase dose as a bar chart. The counts and percentages will also be presented by visit and dose group in supporting summary tables.

A stacked bar chart of hypertensive and diabetes status will be presented for All dose groups combined by Maintenance Phase visit. Diabetes status will be defined as per the definitions in the protocol appendix H and hypertensive status will be defined as per the definitions in the protocol appendix I.

Line plots of Mean HbA1c ± SE over time in the Maintenance and Extended Evaluation Phases will be generated for All dose groups combined by diagnosis of diabetes at Baseline. In addition line plots of the Mean ± SE for all CS comorbidity biomarkers over time in the Maintenance and Extended Evaluation Phases will be presented for All dose groups by Clinical Response status.

Line plots of Mean ± SE of HbA1c and fasting glucose over time in the Maintenance and Extended Evaluation Phases will be generated for All dose groups combined by anti-diabetic drug category. Anti-diabetic drug category will be classed as None, Oral monotherapy only, Oral agent combinations at any time or Insulin at any time.

7.8.2.2 Secondary UFC Analyses

7.8.2.2.1 UFC Response by Visit and Dose

For the ITT, M, MC and PP populations, the UFC response rates will be summarized by visit in the Maintenance Phase, dose group and for All dose groups combined using all three imputation

schemes (as defined in Section 6.6). For the ITT population, subjects who do not enter the Maintenance Phase will be considered as non-responders at each visit.

In addition, for All dose groups combined, the UFC response rates at each visit during the Maintenance Phase will be estimated using the same generalized linear model with repeated measurements described in Section 8.8.1.

The LSMEAN estimate of the UFC response at each visit alongside its Wald 95% CI will be presented as well as the associated standard error. Two-sided p-values for each parameter of the model from the Type III tests of fixed effects will also be presented. Only assessments within the visit window (see Section 6.3) and performed during the Maintenance Phase excluding all follow-up assessments will be included in the analysis.

A supportive analysis that does not require statistical modeling will also be performed at each visit (during the Maintenance and Extended Phases) for All dose groups combined by calculating a Clopper-Pearson two-sided 95% CI for the one-sample binomial proportion.

For the Maintenance Phase the response rate using the 3rd imputation scheme will be displayed on a bar chart by dose group and visit. These bar charts will be repeated for the following subgroup, if they include at least 25% of Maintenance Population:

- Subjects with at least one occurrence of a dose increase (in the Maintenance Phase)

7.8.2.2.2 UFC Improvement by Visit and Dose

The UFC improvement rates will be summarized, analyzed and graphically represented as per the UFC response by visit and dose (see Section 8.8.2.2.1) on the ITT, M, MC and PP populations using all 3 imputation schemes (as defined in Section 6.6).

7.8.2.2.3 Mean, Change From Baseline And Percentage Change From Baseline in Mean UFC

The following summaries and analyses will be performed both on the ITT and MC populations unless specified otherwise.

The mean UFC, change from Baseline in mean UFC and percent change from Baseline in mean UFC will be summarized by study phase, visit and/or dose group and for All dose groups combined.

Paired t-tests comparing the Baseline results to each post-baseline visit in the Maintenance Phase will be performed for All dose groups combined, mean of the difference between Baseline and post-baseline results and its associated 95% CI and two sided p-value from the test will be displayed. The paired t-tests will be performed using SAS® PROC TTEST with PAIRED statement.

In addition, mean UFC, change from Baseline in mean UFC and percent change from Baseline in mean UFC by study phase (Maintenance and Extended Evaluation Phases) will be plotted via line plots by dose group and All dose groups combined.

For the Maintenance and Extended Evaluation Phases, individual by-subject plots (spaghetti) of mean UFC will be plotted by dose group based on the ITT population. A horizontal line will

represent the ULN. In addition, a plot per subject of mean UFC result at each visit (with dose information) will also be presented.

A needle plot representing each subject's mean UFC from Baseline to the End of the Maintenance Phase will also be displayed (subjects in blue will be subjects with a decrease in mean UFC while subjects in red will be subjects with a mean UFC increased). The y-axis will be ordered by the subject's Baseline mean UFC. This display will be produced for the MC population only.

The change from Baseline and percent change from Baseline in mean UFC will be summarized by dose group at Month 6 (or at the last assessed visit in the Maintenance Phase) by Baseline mean UFC category in the M population. Bar charts of mean percentage change $\pm$ SE from Baseline to Month 6 (or at the last assessed visit in the Maintenance Phase) will be produced by dose group and Baseline UFC category. Baseline UFC will be categorized in three strata as follows: 1.5X-<2.0X ULN, 2.0X-<5.0X ULN and ≥5.0XULN.

7.8.2.2.4 Improvement in Mean UFC

The change from Baseline in mean UFC will be categorized as below, and incidence rates for each category will be summarized by study phase, visit and/or dose group and for All dose groups combined on both the ITT and MC populations. Percentages will be based on the number of subjects with an assessment (i.e. have at least one Baseline and post-baseline assessment for the corresponding visit).

- No Improvement: Percent reduction from Baseline < 25%,
- Partial Improvement: Percent reduction from Baseline ≥ 25% and < 50%,
- Improvement: Percent reduction from Baseline ≥ 50% and < 75%,
- Marked Improvement: Percent reduction from Baseline ≥ 75%.

7.8.2.2.5 Shift in Mean UFC abnormalities

The shifts from Baseline in mean UFC relative to the reference range will be summarized at each time point by study phase and dose group and for All dose groups combined on both the ITT and MC populations. The following categorization will be used:

- Less than lower limit of normal (LLN) (< LLN),
- Within the normal range ([LLN; ULN]),
- Greater than ULN and less than or equal to 2x ULN ((ULN; 2 x ULN]),
- Greater than 2x ULN and less than or equal to 5x ULN ((2 x ULN; 5 x ULN]),
- Greater than 5x ULN (>5 x ULN)

For All dose groups combined, two-sided p-values from a generalized McNemar's test (also known as Bowker's test of symmetry) will be provided at each post-baseline visit in the Maintenance Phase to test the paired difference for the shift from Baseline to each post-baseline visit on both the ITT and MC populations. The Bowker's test of symmetry will be performed using SAS® PROC FREQ with TABLES statement and AGREE and TSYMM as option.

In addition, the UFC category relative to the reference will be summarized by dose level and Baseline severity at Month 6 (or the last assessed visit in the Maintenance Phase) in the M population. Counts of the number of responders, the percentage of responders and the Clopper-Pearson two-sided 95% CI will be presented.

7.8.2.3 Serum and Late-night Salivary Cortisol Levels

Serum and mean LNSC levels following 1, 2, 3, 4, 5 and 6 months of dosing in the Maintenance Phase, including change from Baseline and percent change from Baseline will be listed and summarized descriptively by dose group and for All dose groups combined on the ITT and MC populations.

In addition shift tables will be presented for changes from Baseline in LNSC category in the Maintenance and Extended Evauation Phases as follows: >ULN or ≤ULN.

Paired t-tests comparing the Baseline results to each post-baseline visit in the Maintenance Phase will be performed for All dose groups combined on both the ITT and MC populations. Mean of the difference between Baseline and post-baseline results and their associated two-sided 95% CIs and two-sided p-values from the tests will be displayed. The paired t-tests will be performed using SAS® PROC TTEST with PAIRED statement.

Individual and mean LNSC levels will be presented in data listings.

7.8.2.4 Clinical Signs and Symptoms of CS

In addition to the ITT population, the following summaries and analyses will be performed on the MC population.

Summaries of Clinical Signs and Symptoms (as per the eCRF page “Clinical Signs and Symptoms of CS”) will be presented by signs/symptoms and grading by study phase, visit, and/or dose group and for All dose groups combined.

Note: Only the signs and symptoms (moon facies, facial plethora, striae, bruising, supraclavicular fat, menstrual abnormalities – irregular menstruation and menstrual abnormalities – dysmenorrhea, hirsutism, peripheral edema, and acne) as listed in Protocol Amendments 5 and 6 will be included in the analyses. Therefore, only subjects consented under Protocol Amendment 5 or 6 will be included in the summaries/analyses of these endpoints. All signs and symptoms, including those from earlier amendments, will be listed.

The assessment of hirsutism was not described in the protocol as being intended for females only. This was an oversight. Assessment of hirsutism in males is different than in females. The instrument used to collect signs and symptoms was intended for females only. In March 2017, a note was sent to Investigators describing the oversight and asking them to update the study procedures to omit the assessment in males. Analyses of changes in hirsutism will be restricted to females.

Shifts in severity of sign or symptom from Baseline will be provided by study phase, visit, and/or dose group and for All dose groups combined.

For All dose groups combined, two-sided p-values from a generalized McNemar's test will be provided at each post-baseline visit in the Maintenance Phase to test the paired difference for the shift from Baseline to each post-baseline visit. The Bowker's test of symmetry will be performed using SAS® PROC FREQ with TABLES statement and AGREE and TSYMM as options.

As the assessment of the Clinical Signs and Symptoms is based on the date the signs/symptom started/stopped, improved or worsened, each sign/symptom will be slotted in a visit/period based on the following rules:

- For each visit/period (Titration Visit 1, Titration Visit 2, etc. for the Dose Titration Phase, M1 [D30], M2 [D60], M3 [D90], and so on) until subject discontinued or completed the study, for each of the clinical signs/symptoms listed on the eCRF, a grade is assigned. If there was no occurrence of a sign/symptom during a period (for example M1 [D30]) the sign/symptom will be assign a grade of 0 (absence). In addition, for each subject, the Clinical Signs and Symptoms will be plotted.
- If the sign/symptoms started after the stop date of the period or stopped before the start date of the period, the sign/symptom will be associated with a grade of 0 (none/absent).
- If the sign/symptom started (or changed in intensity) before or on the stop date of the period, the sign/symptom will be counted under the last grade recorded for this period (see Table 9 and Figure 2).
- If a visit was not done the subject will not be counted under that visit (for example if M2 [D60] was not done, the subject will be included under M1 [D30] and M3 [D90]).

In the below example (see Table 9 and Figure 2), the clinical sign /symptom of moon facies started on 01JAN2014 and stopped on the 18APR2014. The first dose was on 24JAN2014, so the last grade recorded prior to the date of first dose is 3. At the end of the Titration Visit 1 period (Dose Titration Level 300 mg) the moon facies event is grade 2. The severity of symptom stayed the same until the 31st of March, at the start of the Maintenance Phase (where it decreased to 1). Therefore, during the Dose Titration Phase at each visit, the symptom is summarized under grade 2. At the end of the Maintenance Phase Month 1 (i.e. M1 [D30]), the symptom has a grade of 1 so is summarized under grade 1 at Month 1.

For each subject, the severities for each sign and symptom (graded from 0 = none to 3 = severe) will be summed by visit. Total score and change from Baseline of the severity total score will be presented by visit. Total score will be equal to the sum of the severities for each sign or symptom assessed. To standardize the total scores for the number of signs and symptoms actually assessed, the sum of the individual severity scores will be divided by the number of signs and symptoms actually assessed and multiplied by the maximum number of signs and symptoms assessable at any time on the study. If more than 25% of the individual signs and symptoms have missing scores at a given time point for a subject, then the total score will be set to missing.

Paired t-tests comparing the Baseline results to each post-baseline visit in the Maintenance Phase will be performed for All dose groups combined, mean of the difference between Baseline and post-baseline results and its associated 95% CI and two-sided p-value from the test will be displayed.

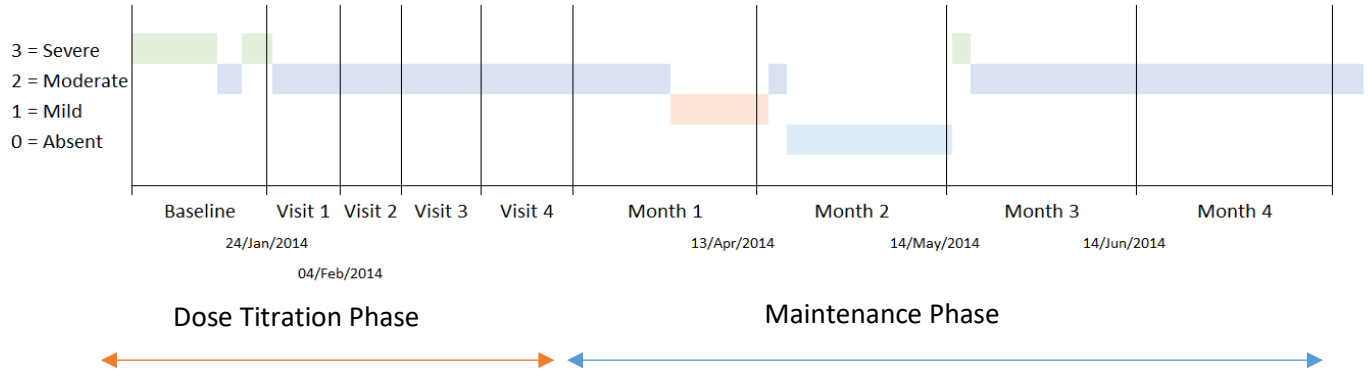
Table 9: Example of Clinical Sign and Symptom of CS aligned per visit (one subject)

Sign/ Symptom	Seq. nb.	Signs/symptom			Interval (Period)				Visit for summary	Grade summarized
		Start date	Stop date	Grade	Visit Start	Start date	Visit Stop	Stop date		
Moon facies	01	01JAN2014	15JAN2014	3	BAS	10JAN2014	BAS	24JAN2014	BAS	
Moon facies	02	16JAN2014	19JAN2014	2	BAS	10JAN2014	BAS	24JAN2014	BAS	
Moon facies	03	20JAN2014	25JAN2014	3	BAS	10JAN2014	Titration # 1	24JAN2014	BAS	3
Moon facies	03	20JAN2014	25JAN2014	3	BAS	25JAN2014	Titration # 1	04FEB2014	Titration # 1	
Moon facies	04	26JAN2014	30MAR2014	2	Titration # 1	25JAN2014	Titration # 1	04FEB2014	Titration # 1	
Moon facies	04	26JAN2014	30MAR2014	2	Titration # 1	05FEB2014	M1 (D1)	14FEB2014	Titration # 2	2
Moon facies	04	26JAN2014	30MAR2014	2	Titration # 1	15FEB2014	M1 (D1)	27FEB2014	Titration # 3	2
Moon facies	04	26JAN2014	30MAR2014	2	Titration # 1	28FEB2014	M1 (D1)	14MAR2014	Titration # 4	2
Moon facies	04	26JAN2014	30MAR2014	2	Titration # 1	15MAR2014	M1 (D1)	13APR2014	M1 (D1)	
Moon facies	05	31MAR2014	15APR2014	1	M1 (D1)	15MAR2014	M1 (D30)	13APR2014	M1 (D1)	1
Moon facies	05	31MAR2014	15APR2014	1	M1 (D1)	14APR2014	M1 (D1)	14MAY2014	M1 (D30)	
Moon facies	06	16APR2014	18APR2014	2	M1 (D1)	14APR2014	M1 (D1)	14MAY2014	M1 (D30)	
Moon facies	07 I	19APR2014	15MAY2014	0	M1 (D1)	14APR2014	M2 (D60)	14MAY2014	M1 (D30)	0
Moon facies	07 I	19APR2014	15MAY2014	0	M1 (D1)	14APR2014	M2 (D60)	14MAY2014	M2 (D60)	
Moon facies	08	16MAY2014	18MAY2014	3	M2 (D60)	15MAY2014	M2 (D60)	14JUN2014	M2 (D60)	

Sign/ Symptom	Seq. nb.	Signs/symptom			Interval (Period)				Visit for summary	Grade summarized
		Start date	Stop date	Grade	Visit Start	Start date	Visit Stop	Stop date		
Moon facies	09	19MAY2014	Ongoing	2	M2 (D60)	15JUN2014	Early Termination*	16JUL2014	M2 (D60)	2
Moon facies	09	19MAY2014	Ongoing	2	M2 (D60)	15JUN2014	Early Termination*	16JUL2014	M3 (D90)	2

* Early Termination occurred after Month 4, no Month 5 period started. Nominal visits used.

Figure 2: Visual representation of the example presented on Table 9.



Baseline Visit: Moon facies – Severe

Visit 1: Moon facies – Moderate

Visit 2: Moon facies – Moderate

Visit 3: Moon facies – Moderate

Visit 4: Moon facies – Moderate

M1 (D30): Moon facies – Mild

M2 (D60): Moon facies – Absent (no symptom of moon facies)

M3 (D90): Moon facies – Moderate

M4 (D120): Moon facies – Moderate

7.8.2.4.1 Visual analog scale questionnaire – subject assessments

As per Protocol Amendment 5, the subject's assessment from the VAS questionnaire are no longer collected. All prior data will be listed by subject and visit.

7.8.2.4.2 Physical signs and proximal myopathy

As of Protocol Amendment 5, the physical signs and proximal myopathy are no longer collected. All prior data will be listed by subject and visit.

7.8.2.4.3 Hirsutism

Total hirsutism score and change from Baseline of total score will be summarized at each visit up to the end of the Maintenance Phase by dose group and for All dose groups combined for female subjects only. Data collected for male subjects will be listed by subject and visit.

7.8.2.4.4 Peripheral edema

Total peripheral edema score and change from Baseline will be summarized at each visit up to the end of the Maintenance Phase, by dose group and for All dose groups combined.

7.8.2.4.5 Acne

Acne global score and change from Baseline in acne global score will be summarized at each visit up to the end of the Maintenance Phase, by dose group and for All dose groups combined.

7.8.2.5 Cushing QoL Questionnaire

Since the Cushing QoL questionnaire is not planned to be assessed during the Dose Titration Phase, all summaries and analyses will be performed on the M population (rather than the ITT population) and the MC population.

Cushing QoL question responses and total standardized derived score will be listed by subject. Quality of life total standardized score and change from Baseline in total standardized score (see Section 6.7.2) will be summarized by visit up to the end of the Maintenance Phase, and by dose group and for All dose groups combined using descriptive statistics.

Paired t-tests comparing the Baseline results to each post-baseline visit in the Maintenance Phase will be performed by dose and for All dose groups combined. Means of the differences between Baseline and post-baseline results and their associated two-sided 95% CI and two-sided p-values from the test will be displayed. The paired t-tests will be performed using SAS® PROC TTEST with PAIRED statement.

7.8.2.6 Beck Depression Inventory II

Since the Beck Depression Inventory II is not planned to be assessed during the Dose Titration Phase, all summaries and analyses will be performed on the M population (rather than the ITT population) and the MC population.

The BDI-II total derived score will be listed by subject.

The BDI-II total score and change from Baseline in total score (see Section 6.7.2) will be summarized by visit up to the end of the Maintenance Phase, and by dose group and for All dose groups combined using descriptive statistics. Only subjects who were enrolled under Protocol Amendment 5 or subsequent amendments will be included in the data summary.

Paired t-tests comparing the Baseline results to each post-baseline visit in the Maintenance Phase will be performed for All dose groups combined, means of the differences between Baseline and post-baseline results and their associated two-sided 95% CI and two-sided p-values from the test will be displayed. The paired t-tests will be performed using SAS® PROC TTEST with PAIRED statement.

Shifts from Baseline in severity of depression (see Section 6.7.2) will be displayed by dose group and for All dose groups combined.

7.8.2.7 Oral Glucose Tolerance Test and Spot Albumin/Creatinine Ratio

Since the OGTT and spot albumin/creatinine ratio are not planned to be assessed during the Dose Titration Phase, all summaries and analyses will be performed on the M population (rather than the ITT population) and the MC population.

OGTT:

Interpretation of the glucose concentration at 2 hours post administration of 75 g of glucose will be summarized for subjects with impaired fasting glucose without diabetes at Baseline. If 75 g of glucose was not administered, any test results will not be interpreted. Individual glucose levels from the 30-min, 60-min, 90-min and 120-min blood samples will be listed in subject data listings. Missing glucose values will not be imputed.

- Normal: 2-hour post-glucose load plasma glucose level is < 140 mg/dL
- Impaired glucose tolerance: 2-hour post-glucose load plasma glucose level >= 140 mg/dL and <= 200 mg/dL
- Provisional diagnosis of diabetes: 2-hour post-glucose plasma glucose level > 200 mg/mL

Incidence of normal, impaired glucose tolerance and diabetic categories, as defined above, from the OGTT results will be summarized at each visit during the Maintenance Phase (including Baseline results) by dose group and All dose groups combined, for subjects with impaired fasting glucose without diabetes at Baseline.

Shifts from Baseline to each category will be summarized for each study phase by dose group and All dose groups combined and by visit.

Glucose values during the OGTT, including changes and percent changes from Baseline, will also be summarized descriptively by maximum value, time to maximum value, and incremental and total areas under the glucose concentration-vs. time-curve calculated using the trapezoidal method.

Paired t-tests comparing the Baseline results to each post-baseline visit in the Maintenance Phase will be performed for All dose groups combined, means of the differences between Baseline and post-baseline results and associated two-sided 95% CI and two-sided p-values from the tests will be displayed. The paired t-tests will be performed using SAS® PROC TTEST with PAIRED statement.

Overlaying individual line plots of glucose concentration over time will be presented for each dose level.

Spot Albumin/Creatinine Ratio:

Spot albumin/creatinine ratio values were obtained from subjects with abnormal values at Baseline. Ratio values and changes from Baseline will be summarized descriptively for each study phase by visit up to the end of the Maintenance Phase. Paired t-tests comparing the Baseline results to each post-baseline visit in the Maintenance Phase will be performed for All dose groups combined, means of the differences between Baseline and post-baseline results and associated two-sided 95% CI and two-sided p-values from the tests will be displayed. The paired t-tests will be performed using SAS® PROC TTEST with PAIRED statement.

Incidence of abnormal results (i.e. outside of the normal range) will be summarized for each study phase by visit (and at any visit during the study phase) and by dose group and for All dose groups combined.

Shifts from Baseline from the normal range (Low, Normal, High and abnormal [low/high]) will be summarized for each study phase by dose group and visit.

The mean ± SE will be plotted at each visit of Maintenance Phase by dose group and for All dose groups combined.

7.8.2.8 C-reactive Protein

In addition to the ITT population, all summaries and analysis will be presented on the MC population.

C-reactive protein is considered as a CS comorbidities biomarker and will be summarized and analyzed as described in Section 8.8.2.1. In addition, the following summaries and plots will be produced:

Incidence of abnormal results (i.e. outside of the normal range) will be summarized for each study phase by visit and/or dose group and for All dose groups combined.

Shift from Baseline from the normal range (Low, Normal, High and abnormal [low/high]) will be summarized for each study phase by visit and/or dose group and for All dose groups combined.

The mean ± SE will be plotted at each visit of Maintenance Phase for All dose groups combined and by dose group.

7.8.3 Exploratory Efficacy Endpoints and Analyses

All summaries and analyses below will be presented for the ITT population. For exploratory efficacy endpoints for the Extended Evaluation Phase that have secondary efficacy endpoint counterparts for the Maintenance Phase, the same univariate tests (e.g. paired t-test, Wilcoxon signed rank test) that will be used to analyze the secondary endpoints wil also be used to analyze the exploratory endpoints; however, the p-values for the exploratory efficacy endpoints are considered to be descriptive only.

7.8.3.1 Exploratory Urinary Free Cortisol Analyses

The UFC response rates and UFC improvement rates at 9 and 12 months of dosing in the Extended Evaluation Phase will be summarized by dose group and for All dose groups combined as described in Section 8.8.2.2.1 and Section 8.8.2.2.2. There will be no imputation of missing data, and the response or improvement will be assessed regardless of dose increase.

Mean, change from Baseline and percentage change from Baseline in mean UFC for the Extended Evaluation Phase will be similarly presented as described in Section 8.8.2.2.3. Shift in UFC normality categories from Baseline at 9 and 12 months of the Extended Evaluation Phase will be considered as mentioned in Section 8.8.2.2.5.

7.8.3.2 Exploratory Late Night Salivary and Serum Cortisol Levels Summaries

Serum cortisol levels and mean LNSC levels at 9 and 12 months of dosing in the Extended Evaluation Phase including change from Baseline and percent change from Baseline will be listed and summarized descriptively by dose group and for All dose groups combined.

The normalization of LNSC (i.e., percentage of subjects with LNSC ≤ ULN) over time in the Maintenance and Extended Evaluation Phases will be presented as a bar chart by dose group and all dose groups combined.

Individual serum cortisol levels will be presented in data listings.

7.8.3.3 Exploratory Clinical Signs and Symptoms of Cushing's Syndrome, Cushing Quality of Life and Beck Depression Inventory II Summaries

Summaries will be presented at each visit in the Extended Evaluation Phase by signs/symptoms and grading for each dose group and for All dose groups combined. Change from Baseline summaries will be presented for clinical signs and symptoms of CS, QoL scores and BDI-II total score.

Clinical signs and symptoms of CS in the Maintenance and Extended Evaluation Phases will be summarized graphically through individual subject-time profile of the preferred terms and

severity, time profile of the preferred terms and median severity, and percentage of subjects with an improvement from Baseline at Month 6 (or the last assessed visit in the Maintenance Phase) by mean UFC category at Month 6 (or the last assessed visit in the Maintenance Phase) and overall.

7.8.3.4 Exploratory Cushing's Syndrome Comorbidities Biomarkers Summaries

The change from Baseline in CS comorbidities biomarkers results at 9 and 12 months of dosing in the Extended Evaluation Phase will be summarized at each time point by dose group and for All dose groups combined.

7.8.3.5 Exploratory Oral Glucose Tolerance Test and Spot Albumin to Creatinine Ratio Summaries

Change from Baseline in glucose values from the OGTT for pre-diabetics subjects at Baseline and spot albumin ratio values at 9 and 12 months will be summarized descriptively.

7.8.3.6 Exploratory C-reactive Protein Summaries

Change from Baseline in CRP values will be summarized descriptively at 9 and 12 months of dosing in the Extended Evaluation Phase.

7.8.3.7 Clinical Benefit

The proportion of subjects achieving Clinical Benefit (see Section 6.7.2) and Clopper-Pearson two-sided 95% CIs for the Maintenance Phase and Extended Evaluation Phase will be displayed in tables and graphically by visit, dose group and for All dose groups combined for all subjects reaching the Maintenance Phase.

The summary and graphical representation of the Clinical Benefit will be repeated using two alternative definitions of Clinical Benefit (Clinical Benefit regardless of dose increase and Clinical Benefit with partial UFC normalization, regardless of complete response status; see Section 6.7.2 for their definitions).

Only subjects with an abnormal value at Baseline for one or more of the 8 pre-specified CS comorbidities biomarkers (fasting glucose, HbA1c, SBP, DBP, total cholesterol, LDL-C, HDL-C, body weight) will be included in the analysis of Clinical Benefit, since one of the criteria for Clinical Benefit requires the presence of one or more abnormal values at Baseline.

7.8.3.8 Medication Changes

Throughout the study, the Investigators record all medications taken by subjects and any changes. A new record is created to document a change either in dose or frequency or new drug. Medications with the same preferred term will be categorized as the same medication. Using the start date of each record the medication changes will be segmented by study phase.

- **Dose increase**: for a continuing medication, after the first dose of study drug, there is a

new record with a total daily dose that is above the total daily dose from the prior medication record.

- **Dose decrease**: for a continuing medication, after the first dose of study drug, there is a new record with a total daily dose that is below the total daily dose from the prior medication record.
- **New medication**: a medication that started after the first dose of study drug and for which no same medication was taken at Baseline.
- **Discontinued medication**: a medication that has stopped after the first dose of the study drug, and no more records of that drug indicating restarts are present.

The above categories are not mutually exclusive.

The number and percentage of subjects with medication changes for blood pressure, diabetes and cholesterol management in each phase of the study, will be summarized for each of the following possible categories.

- Condition improving,
- Condition worsening,
- Study drug interaction,
- Other (non-study) drug interaction,
- Investigator decision,
- Other.

Summaries will be presented for each study phase by dose group and for All dose groups combined (i.e. considering all new medications started after the 1st dose of study drug).

The relationship between change in co-medications (antihypertensive drugs, anti-diabetic drugs and cholesterol-lowering drugs) and change in the associated biomarkers of comorbidity of CS (SBP and DBP, fasting glucose, HbA1c, Total Cholesterol, HDL-C and LDL-C) will be investigated. For this purpose, the following by-subject profile will be provided within each study phase:

On the top of the page the clinical assessment will be plotted per study day while on the 2nd half of the page, associated medications will be listed (includes name of the medication, start/stop date, total daily dose and unit as well as frequency and route of administration).

- SBP and DBP vs antihypertensive drugs
- Fasting Glucose vs. anti-diabetic drugs
- HbA1c vs. anti-diabetic drugs
- Total Cholesterol, HDL-C and LDL-C vs. anti-hypercholesterolemia drugs

Use of anti-diabetic drugs will be summarized in a bar chart for All dose groups by drug class. Drug class will be one of the following: Biguanides (metformin), Insulins, Glinides, Sulfonamides, TZD, Gliptins and Gliflozins.

The counts and percentages will also be presented in a supporting summary table.

7.8.3.9 Clinical Signs of Hypercortisolism Assessed through Standardized Photographs

An independent adjudication committee, composed of three clinician-investigator experts in CS will assess the subjects for changes in visible signs of hypercortisolism (moon face, plethora, supraclavicular and dorsal fat pads, striae, hirsutism, bruising and overall body habitus) by scoring standardized photographs. The scoring will be based on overall subjective impression of changes from Baseline to M3 (D90) visit, End of Maintenance Phase visit and End of Extended Evaluation Phase visit, as follows: obvious visible worsening, subtle visible worsening, no visible changes, subtle visible improvements, obvious visible improvements.

Shift tables of the scores from Baseline will be presented by dose group and for All dose groups combined. The denominator of the percentages will be considered the number of subjects who consented to the photographs and for which the photographs were evaluated by the specialists at both Baseline and each of the corresponding visits.

7.8.3.10 Intra-subject Within-visit Variability

For each of the following assessments, for each subject, the SD will be calculated at each visit where more than one planned assessment is recorded in Maintenance and Extended Evaluation Phases. The SDs will be summarized for All dose groups combined.

- UFC
- LNSC
- SBP and DBP
- Abdominal girth

7.8.4 Other Exploratory Analysis

Analysis of subject response in each of the categories defined below will be performed at all visits during the Maintenance Phase and the Extended Evaluation Phase.

7.8.4.1 Diabetes Mellitus Responders

For the subpopulation of subjects meeting any of the following conditions at Baseline: (1) a confirmed diagnosis of diabetes mellitus and on anti-diabetic treatment, or (2) a fasting glucose of ≥126 mg/dL (7.0 mmol/L), or (3) a 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 (i.e. during OGTT), or (4) HbA1C ≥6.5% (48 mmol/mol), summary statistics of Diabetes mellitus responders will be provided.

Diabetes mellitus responders are defined as (1) subjects with absolute HbA1C reduction of at least 0.3 percentage points from Baseline without increases in dose(s) of continuing anti-diabetic medications or the addition of new anti-diabetic medication(s), OR (2) subjects with a total daily dose reduction of at least 50% of any continuing anti-diabetic medication, without new anti-diabetic medication or an increase in dose of any anti-diabetic medication, OR (3) subjects not

treated with anti-diabetic medications at Baseline and with an HbA1C reduction of at least 0.3 percentage points and who have not started taking new anti-diabetic medication.

7.8.4.2 Hypertensive Responders

For the subpopulation of subjects with SBP of greater or equal to 140 mmHg (with or without antihypertensives) or normal BP and on antihypertensive medication at Baseline, summary statistics of hypertensive responders will be summarized.

A hypertensive responder is defined as a subject with (1) a reduction in SBP or DBP of at least 2 mmHg from Baseline. Responders must have also either maintained a stable dose OR had a reduction in dose OR withdrawal of continuing antihypertensive medications. If not treated with antihypertensive medication at Baseline they must not have been started on new antihypertensive medication.

7.8.4.3 Hypercholesterolemia Responders

For the subpopulation of subjects with either of the following conditions met at Baseline (1) a LDL-C > 3.3 mmol/L (129 mg/dL) and not receiving statin therapy; or (2) LDL-C >2.6 mmol/L (100 mg/dL) and receiving statins; summary statistics of hypercholesterolemia responders will be provided.

Hypercholesterolemia responders are defined as (1) subjects with a relative reduction from Baseline in LDL-C of at least 24% and without a corresponding relative decrease in HDL-C of greater than 12% or an increase in dose of continuing cholesterol-lowering medication or the addition of new cholesterol-lowering medications, OR (2) subjects with a reduction of at least 50% of the total daily dose of any continuing cholesterol-lowering medication or withdrawal of cholesterol-lowering medications and LDL-C <3.3 mmol/L, OR (3) subjects not treated with cholesterol-lowering medication at Baseline with a relative reduction LDL-C of at least 24% from Baseline and did not add a new cholesterol-lowering medication.

7.8.4.4 Obesity Responders

For the subpopulation of obese subjects at Baseline (BMI > 30), summary statistics of obesity responders will be provided.

An obesity responder is defined as a subject with a relative decrease in body weight of 5% from Baseline OR with normalization of BMI (BMI ≤ 25) at the end of the Maintenance Phase. Concomitant use of weight-loss medications was excluded by protocol. Subjects who deviated from the protocol and used weight-loss medications at Baseline or during the study will not be considered obesity responders regardless of changes in body weight or BMI.

7.8.4.5 Metabolic Syndrome Responders

For the subpopulation with metabolic syndrome at Baseline, summary statistics of metabolic syndrome responders will be provided. The international harmonized definition of metabolic

syndrome (2009) will be used, as summarized here. At least 3 of the following 5 criteria must be present to have the metabolic syndrome:

1. Waist circumference: Men ≥ 102 cm; women ≥ 88 cm
2. Serum fasting triglyceride ≥ 150 mg/dL (1.7 mmol/L) OR currently using one or more of the following drug classes: fibrates, niacin or high-dose omega-3 fatty acids
3. Serum HDL-cholesterol < 40 mg/dL (1.0 mmol/L) in males; > 50 mg/dL (1.3 mmol/L) in females
4. SBP ≥ 130 and/or DBP ≥ 85 mm Hg OR currently receiving antihypertensive drug therapy
5. Serum fasting glucose ≥ 100 mg/dL (5.5 mmol/L) OR currently receiving anti-diabetic drug therapy.

A metabolic syndrome responder is defined as a subject who met the definition of metabolic syndrome at Baseline as defined above and no longer meets the definition of metabolic syndrome at the end of the Maintenance Phase.

7.9 *PHARMACOKINETIC/ PHARMACODYNAMIC ENDPOINTS AND ANALYSES*

7.9.1 Pharmacokinetic Endpoints and Analyses

Population PK endpoints and analyses will be discussed in a separate population PK/PD analysis plan.

7.9.2 Pharmacodynamic Endpoints and Analyses

Population PD endpoints and analyses will be discussed in a separate population PK/PD analysis plan.

7.10 *QUALITY OF LIFE OR PHARMACOECONOMIC ENDPOINTS AND ANALYSES*

For the QoL questionnaire see Section 6.7.2 and Section 8.8.2.5.

7.11 *SAFETY DATA ENDPOINTS AND ANALYSES*

All Safety analyses will be performed on the ITT Population. In addition, selected safety summaries will be presented for the DT and MC populations, as described below.

7.11.1 Adverse Events

All AEs will be coded using MedDRA dictionary and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI-CTCAEv4).

All information on AEs will be listed by subject.

All reported TEAEs will be summarized.

All TEAEs will be assigned to only one study phase (Dose Titration, Maintenance or Extended Evaluation Phase) based on the start date of the phase and start date of the TEAE. TEAEs will be summarized per dose group and for All dose groups combined for each study phase and for the Maintenance and Extended Evaluation Phases combined. TEAEs will also be summarized for All phases combined for All dose groups combined only.

For the Dose Titration Phase, subjects will be summarized under each dose level they reached during the Dose Titration Phase, and a TEAE for a subject will be assigned to the last dose level the subject received on or before the start of the TEAE. For the Maintenance Phase, subjects will be summarized under their Therapeutic Dose. For the Extended Evaluation Phase, subjects will be summarized under each dose level they received during the Extended Evaluation Phase, and a TEAE for a subject will be assigned to the last dose level the subject received on or before the start of the TEAE. For the Maintenance and Extended Evaluation Phases combined, subjects will be summarized under their Therapeutic Dose.

An overview of TEAE incidence rates by categories (see below) will be provided. In addition, the total number of events will be summarized. A unique event for a subject is defined as a unique combination of subject, system organ class, preferred term, AE start date, severity, and relationship to study drug. Clopper-Pearson two-sided 95% CIs of the incidence rates will be provided for All dose groups combined and for each of the TEAE categories below.

The frequencies in these analyses, represented as percentages, will be calculated as the number of subjects reporting at least one AE in each dose group divided by the total number of subjects in each dose group at any time during the study phase.

- TEAE
  - Any TEAE
  - Any study drug related (i.e. probable or definitely related as per the Investigator) TEAE
  - Any TEAE leading to study drug discontinuation
  - Any TEAE with worst severity of Severe
  - Any TEAE with worst severity of Moderate
  - Any TEAE with worst severity of Mild
  - Any non-serious TEAE of Special Interest

- Serious TEAE
  - Any SAE

- Any study drug related SAE
- Any SAE leading to study drug discontinuation
- Any SAE with worst severity of Life Threatening
- Any SAE with worst severity of Severe
- Any SAE with worst severity of Moderate
- Any SAE with worst severity of Mild
- Any SAE leading to death
- Any study drug related SAE leading to death
- Any SAE of Special Interest.

AEs of special interest, as defined per protocol, will be flagged in the eCRF by the Investigator and are:

- Persistent QTc prolongation events,
- Potential hepatic events,
- Adrenal Insufficiency events.

Note that AESIs are ultimately categorized by the Investigator, even if the Sponsor's medical monitor does not agree with the assignment.

The following category of AEs will be derived from the preferred terms. The list of preferred terms will be provided by the Cmed Medical Monitor and reviewed and approved by a Cortendo Study Physician. A separate summary table will be produced.

- TEAEs potentially associated with abnormality of cardiac repolarization (syncope, dizziness, palpitations, etc.)

The following summaries of TEAEs will be provided by System Organ Class and Preferred Term and by dose group and for All dose groups combined. The System Organ Classes and the Preferred Terms within each System Organ Class will be presented in order of decreasing frequency for All dose groups combined.

- Incidence of TEAEs
- Incidence of drug-related TEAEs
- Incidence of TEAEs by worst severity
- Incidence of TEAEs leading to study drug discontinuation
- Incidence of drug-related TEAEs leading to study drug discontinuation
- Incidence of TEAEs of special interest
- Incidence of serious TEAEs
- Incidence of serious TEAEs by worst severity

A summary of TEAE by System Organ Class and Preferred Terms will be provided for events with an incidence rate of at least 5% for All dose groups combined (i.e. summarizing the most common AEs). In addition, for this summary, Clopper-Pearson two-sided 95% CI will be provided for All dose groups combined.

For any TEAE with an overall incidence > 10%, the following split by subgroups will be investigated:

- Age (rounded median split),
- Sex,
- Disease duration (category)

Subjects will be counted only once within each System Organ Class, Preferred Term and Severity.

- If there is more than one AE within the same System Organ Class, the subject will be counted only once in that System Organ Class.
- If there is more than one AE coded to the same Preferred Term within a System Organ Class, the subject will be counted only once in that System Organ Class and Preferred Term.
- If there is more than one AE coded to the same Preferred Term within a System Organ Class, the subject will be counted only once in that System Organ Class and Preferred Term under the worst severity. Worst severity is ordered from most to least severe as follows: Death, Life-threatening, Severe, Moderate, and Mild.

If an AE severity is missing for a subject, its grade will be imputed as the worst grade reported for that subject (across all AEs) between mild, moderate, severe and life-threatening (i.e. excluding death).
If there is any subject for which all of the AEs have a missing severity, then the "Missing" category will be considered as the lowest/worst severity grade (i.e. below Mild).

If the relationship for an AE is missing it will be assumed to be related to study drug in the summary tables.

All AEs will be listed by subject; pre-existing conditions (i.e. AEs which are not treatment-emergent) and TEAEs will be flagged.

The following AEs will be listed:

- All AEs
- SAEs
- Adverse events leading to study drug discontinuation
- Adverse events leading to death
- Adverse events of special interest

An overview of TEAE table and a TEAE table by system organ class and preferred term will be produced for the DT population. There will no statistical tests of the TEAEs for the DT population.

7.11.2 Clinical Laboratory Evaluations

Laboratory analytes (hematology, blood chemistry, urinalysis, coagulation) values and change from Baseline will be summarized descriptively for each study phase by visit and/or dose group and for All dose groups combined. For Hematology, Blood Chemistry and Coagulation parameters these summaries will be repeated using the DT population.

For each analyte, incidence of abnormal results (i.e. outside of the normal range) will be summarized for each study phase by visit (and at any visit during the study phase) and/or dose group and for All dose groups combined. This summary by study phase will include unscheduled visits. A listing of all laboratory analytes and their corresponding normal ranges will be produced.

For each analyte, shift from Baseline from the normal range (Low, Normal, High and Abnormal [low/high]) will be summarized for each study phase (including unscheduled visits) and by visit and/or dose group. For Hematology and Blood Chemistry analytes these summaries will be repeated using the DT population.

In addition, for liver test analytes (Aspartate Aminotransferase [AST], Alanine Aminotransferase [ALT], Alkaline Phosphatase, Gamma-glutamyl Transferase [GGT] and Total Bilirubin), the results will be tabulated by study phase, visit (including unscheduled visits) and/or dose group and for All dose groups combined. A shift table will also be presented by study phase, visit and/or dose group and for All dose groups combined. The below categories will be used for incidence summaries and shift tables for LFTs (except Total Bilirubin):

- Less than LLN (< LLN)
- Within the normal range ([LLN; ULN])
- Greater than ULN and less than or equal to 3x ULN ((ULN; 3 x ULN]),
- Greater than 3 x ULN and less than or equal to 5x ULN ((3 x ULN; 5 x ULN]),
- Greater than 5 x ULN and less than or equal to 10x ULN ((5 x ULN, 10 x ULN]),
- Greater than 10 x ULN (> 10 x ULN).

For Total Bilirubin, the below categories will be used for incidence summaries and shift tables:

- Less than LLN (< LLN)
- Within the normal range ([LLN; ULN])
- Greater than ULN and less than or equal to 2 x ULN ((ULN; 2 x ULN]),
- Greater than 2 x ULN (> 2 x ULN)

The number of subjects with International Normalized Ratio (INR) >1.5 by study phase, visit, and/or dose group will also be summarized. This will be repeated for the DT Population for the Dose Titration Phase only.

Furthermore, box-and-whisker plots of results by study phase, visit, and/or dose group and change from Baseline will also be produced for each LFT and electrolyte parameter. These box-and-whisker plots will be repeated using the DT population.

A matrix of eDISH plots for all ALT, AST, and Total Bilirubin results (regardless of time point) divided by their respective ULN will be plotted. In eDISH plots the x- and y-axes are on a log/log scale and the LFT results are plotted as multiples of the ULNs of the LFTs.

The following six individual-subject eDISH plots will be presented by study phase and for the Dose Titration Phase and Maintenance Phase combined:

- Baseline ALT (expressed as x ULN) x Maximum Post-baseline ALT (expressed as x ULN)

- Maximum Post-baseline ALT (expressed as x ULN) x Maximum Post-baseline AST (expressed as x ULN)
- Maximum Post-baseline ALT (expressed as x ULN) x Maximum Post-baseline Total Bilirubin (expressed as x ULN)
- Baseline AST (expressed as x ULN) x Maximum Post-baseline AST (expressed as x ULN)
- Maximum Post-baseline AST (expressed as x ULN) x Maximum Post-baseline Total Bilirubin (expressed as x ULN)
- Baseline TBILI (expressed as x ULN) x Maximum Post-baseline Total Bilirubin (expressed as x ULN)

For ALT, AST and Total Bilirubin, all post-baseline values during the study phase of interest will be included in determining the maximum post-baseline values for that study phase.
Different symbols and colors will be used to distinguish the dose levels on the individual-subject scatterplots.

Individual-subject line plots (*or line plot matrices if possible*) will be presented showing the time course of LFT values for all LFTs only for subjects where the maximum value of ALT or AST exceeds 3 X ULN and 5 x ULN or the maximum value of Total Bilirubin exceeds 2 X ULN at anytime during the study.

The time to the incidence of the maximum post-baseline value > 3 x ULN for each LFT (except Total Bilirubin) and > 2 x ULN for Total Bilirubin will be presented versus the probability of incidence as Kaplan-Meier curves by study phase and dose group. The y-axis will present the Kaplan-Meier estimates of the cumulative probabilities of no event, and the x-axis will present the study day relative to the first dose of COR-003 in the study phase being presented. A corresponding summary table of the Kaplan-Meier estimates for mean, median, and quartile times to incidence as well as cumulative probabilities of no event at specific study days of interest will be produced.

All data will be listed in subject data listings and abnormal results will be flagged.

7.11.3 Hormones and Biomarkers Laboratory Evaluations

For certain hormones and biomarker laboratory parameters (triglycerides, LDL-C/HDL-C ratio, TSH, Free T4, IGF-1 and testosterone concentrations) values and change from Baseline will be summarized descriptively for each study phase by visit and/or dose group and for All dose groups combined.

ACTH values and change from Baseline values will summarized descriptively for each study phase by visit and/or dose group and for All dose groups combined for all subjects combined and also for just subjects with an etiology of ACTH-dependent CS, subcategorized as CD only and ectopic ATCH only. This summary will be repeated for the DT and MC populations.

For each analyte, the incidence of abnormal results (i.e. outside of the normal range) will be summarized for each study phase (and at any visit during the study phase) (including unscheduled visits) and by visit and by dose group and for All dose groups combined.

For each analyte, shift from Baseline (Low, Normal, High and abnormal [low/high], defined by the normal range) will be summarized for each study phase (including unscheduled visits) and by visit and/or dose group and for All dose groups combined.

7.11.4 Vital Signs

Temperature, HR and three measurements of SBP and DBP were to have been collected at each visit.

Vital sign (Height, HR, Sitting Blood Pressure [SBP and DBP], Body Temperature) values and changes from Baseline will be summarized descriptively for each study phase by visit and/or dose group and for All dose groups combined.

Shifts from Baseline for each of the vital signs specified in Table 10 will be summarized for each study phase (including unscheduled visits) and by visit, dose group and for All dose groups combined.

Table 10: Vital sign categories for shift tables

Vital Sign	Category	Flag
Heart Rate	< 44 bpm	Low (L)
	44-100 bpm	Normal
	101-120 bpm	High (H)
	>120 bpm	Very High (VH)
	< 44 bpm or >100 bpm	Abnormal (A)
Systolic Blood Pressure	< 90 mmHg	Low (L)
	90-139 mmHg	Normal
	140-169 mmHg	High (H)
	≥170 mmHg	Very High (VH)
	< 90 mmHg or > 139 mmHg	Abnormal (A)
Diastolic Blood Pressure	< 50 mmHg	Low (L)
	50-89 mmHg	Normal
	90-109 mmHg	High (H)

Vital Sign	Category	Flag
	≥ 110 mmHg	Very High (VH)
	< 50 mmHg or > 89 mmHg	Abnormal (A)

All vital signs will be listed by subject and visit and abnormal results as per criteria defined in Table 10 will be flagged.

As of Protocol Amendment 5, Ambulatory blood pressure (i.e. BP measured outside of clinic) is no longer measured; ambulatory BP data collected will be listed by subject and visit and not summarized.

7.11.5 Electrocardiograms

Quantitative ECG measurements (PR interval, QRS duration, HR, uncorrected QT interval, QT interval corrected using Bazett's correction (QTcB interval), and QT interval corrected using Fridericia's correction (QTcF interval) and changes from Baseline will be summarized descriptively by study phase, visit, and/or dose group. Paired t-tests comparing the Baseline results to each post-baseline visit will be performed for All dose groups combined, means of the differences between Baseline and post-baseline results and associated two-sided 95% CI and two-sided p-values from the tests will be displayed. The paired t-tests will be performed using SAS® PROC TTEST with PAIRED statement.

The number and percentage of subjects with notable PR interval, QRS duration, uncorrected QT interval, QTcB interval, and QTcF interval will be summarized for each study phase by dose group and visit (and at any visit during the study phase). Notable results are defined as per Table 11a.

In addition, shifts from Baseline in overall interpretation (normal, abnormal not clinically significant and abnormal clinically significant) will be tabulated by study phase and dose group for each post-baseline visit and displayed.

For All dose groups combined, two-sided p-values from the McNemar's paired comparison test will be provided for the shift from normal to not clinically significant or clinically significant abnormal values. The McNemar's tests will be performed using SAS® PROC FREQ with EXACT statement and MCNEM options.

Box-and-whisker plots will be produced to graphically represent the QTcF interval results and changes from Baseline at each visit by dose group (Dose Titration and Maintenance/Extended Evaluation Phases will be separated).

ECG interval values will be listed by subject and visit. Notable results will be flagged as per criteria defined in Table 11a and summarized by study phase, dose group, and visit (for the Maintenance and Extended Evaluation Phases). The clinical abnormalities based on the overall interpretation will also be flagged.

Table 11a: Notable ECG Criteria

Parameter	Criteria
QTc, QTcB, QTcF	> 450 msec
	> 480 msec
	> 500 msec
	> 30 msec from Baseline
	> 60 msec from Baseline
PR	≥ 50% increase from Baseline if Baseline < 200 ms
	≥ 25% increase from Baseline if Baseline ≥ 200 ms
QRS	≥ 50% increase from Baseline if Baseline < 110 ms
	≥ 25% increase from Baseline if Baseline ≥ 110 ms

QTcF categories (L, M or H, as described in Table 11b) will be used to summarize QTc by worst (greatest) QTcF interval change from Baseline and worst (greatest) actual value per study phase by dose group and all dose groups combined for the ITT population and in the Dose Titration Phase for the DT population. These categories will be used for descriptive summaries and listings. The summaries will include the Baseline mean and median QTcF values.

Table 11b: QTcF Interval Values for Additional Analyses

QTcF Interval	Criterion (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)

7.11.6 Physical Examination Findings

Clinically significant physical examination findings found after the first dose of COR-003 were to be reported as AEs by the Investigators and will be summarized as AEs.

7.11.7 Other Safety Measures

Pituitary diameter (mm) and pituitary volume (mm^3) will be summarized at Baseline and by study phase (Maintenance and Extended Evaluation), by dose group and for All dose groups combined. The summary will be provided only for subjects with CD at Baseline. Change from Baseline will also be summarized. Pituitary volume will be derived as π/6 times maximum pituitary height x length x width in mm^3 ($V=\pi/6 \times hlw$). The maximum height (h) is the larger of the coronal height and sagittal height. The length (l) and width (w) are the sagittal length and coronal width, respectively.

Results from pituitary MRI will be listed by subject and visit.

7.12 *Subgroup Analysis*

Subgroup summaries/analysis will be performed on the ITT population using the following subgroups. For each individual subgroup, if a subject has missing/unknown results, the subject will be excluded from the subgroup summaries/analysis (for example, if the age of a subject is missing / unknown the subject will be excluded from the by-age summaries/analyses). Subgroup summaries will only be performed for a minimum subgroup size of at least 30% of the ITT population, unless otherwise specified. P-values from statistical tests will be considered as descriptive rather than inferential. The following subgroups will be considered for analysis.

- Cushing's Disease
  - With CD – Subjects with CD as recorded in the CRF at Baseline,
  - Without CD (any other form of CS)
- Prior Therapy for CS (3 sets of mutually exclusive subgroups)
  - Therapy-naïve versus not therapy-naïve (any prior drug therapy or surgery for CS)
  - Prior drug therapy versus No prior drug therapy
  - Prior surgery versus No prior surgery (applicable only to CD subjects)
- Prior Radiation Therapy
  - Subjects without previously received radiation therapy
- Hypertensive Subjects
  - Subjects with diagnosed Hypertension at Baseline, according to CRF response
  - Subjects without diagnosed Hypertension at Baseline, according to CRF response
- Diabetes Status at Baseline
  - Subjects without diagnosed prediabetes or diabetes
  - Pre-Diabetes Subjects, according to CRF response (inclusion criterion 9)
  - Diabetic Subjects, according to CRF response
- Region
  - US
  - non-US
- Sex
- Age

  - ≤ Median
  - > Median
- Time since CS diagnosis (note: the categories may be changed if the sample sizes are not adequate for some of the subgroups.)
  - < 2 years
  - 2 to <10 years
  - ≥ 10 years
- Baseline UFC by tertiles
- Baseline LNSC by tertiles
- Baseline ACTH by tertiles

The endpoints to be analyzed by subgroup are defined below in Table 12.

The subgroup analysis of efficacy endpoints by visit during the Maintenance Phase by Baseline UFC tertiles will address the part of the primary objective on evaluating the range of effective doses in subjects with various levels of hypercortisolism, since the by-visit summaries present the results by the Therapeutic Dose groups.

Table 12: Analyses by subgroup

Output	Subgroup											
	Cushing's Disease	Prior Therapy for CS	Prior Radiation Therapy	Hypertensive subjects	Diabetes Status	Region	Sex	Age	Time since CS Diagnosis	Baseline UFC	Baseline LNSC	Baseline ACTH
Demographics and Baseline Characteristics	X	X		X	X	X	X	X	X	X	X	X
Study Drug Exposure and Compliance	X					X						
Summaries and Primary Analysis of Clinical Response	X	X	X	X	X	X	X	X	X	X	X	X
Summaries and bar charts of UFC Response and Improvement	X	X				X	X	X	X	X	X	X
Summary of Change from Baseline in Mean UFC	X											
Plots of Mean Change and Percentage Change from Baseline in Mean UFC	X											
Summary of CS Comorbidities Biomarkers	X		X	X	X	X	X	X	X	X	X	X
Summary of Change and Percent Change from Baseline CS Comorbidities Biomarkers	X		X	X	X	X	X	X	X	X	X	X
Summary of Clinical Signs and Symptoms of CS	X					X	X	X	X	X		

Summary of Change from Baseline in Clinical Signs and Symptoms of CS	X					X	X	X	X	X		
Summary of Total Peripheral Edema Score by Visit	X			X	X	X	X	X	X	X		
Summary of Change from Baseline in Total Peripheral Edema Score by Visit	X			X	X	X	X	X	X	X		
Summary of Acne Global Score by Visit (female only)	X					X		X		X		
Summary of Change from Baseline in Acne Global Score by Visit (female only)	X					X		X		X		
Summary of Cushing QoL Total Score by Visit	X			X	X	X	X	X	X	X		
Summary of Change from Baseline in Cushing QoL Total Score by Visit	X			X	X	X	X	X	X	X		
Summary of Total BDI-II Score by Visit	X			X	X	X	X	X	X	X		
Summary of Change from Baseline in Total BDI-II Score by Visit	X			X	X	X	X	X	X	X		
Summary of Mean LNSC	X	X				X	X	X	X	X	X	X
Summary of Change from Baseline in Mean LNSC	X	X				X	X	X	X	X	X	X
Overall Summary of TEAEs	X	X		X	X	X	X	X	X	X	X	X
Incidence of TEAEs by System Organ Class and Preferred Term						X	X	X		X	X	X

8 Timing of Analysis and Reporting

Final data analysis will be performed in two separate stages: (1) the end of the Maintenance Phase and (2) at the end of the Extended Evaluation Phase.

The final analysis of safety is 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), including the Follow-up visit. Interim analyses of safety are planned to coincide with timing for the primary analysis of efficacy (i.e. after the last subject has completed the 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 Data Safety Monitoring Board (DSMB) will review all SAEs and adverse events of special interest (AESIs) on a rolling basis and assess benefits and risk of therapy systematically at approximately 6-month intervals. These analyses are detailed separately in the DSMB SAP.

Once all data are available for analysis of the primary endpoint, at the End of the Maintenance Phase, those data will be locked (Data lock 1). There will be a second lock after the Extended Evaluation Phase when the study is completed. (Data lock 2)

- **End of Maintenance Phase Analysis:** This analysis will be conducted after the last subject is assessed for efficacy after 6 months in the Maintenance Phase. The data will be locked for all visits prior to and including the End of Maintenance Phase visit (and Follow-up visit for early withdrawal or irradiated subjects). For the data collected on an ongoing basis (i.e. not linked to visits) the data will be cleaned / reconciled and reported, up to the End of the Maintenance Phase. All visits and events reported during the Maintenance Phase, including the primary analysis, will be reported once all subjects have completed the Maintenance Phase. In addition, all SAEs occurring during the Extended Evaluation Phase but recorded in the database prior to the End of Maintenance Phase Analysis will be preliminarily summarized for the End of Maintenance Analysis in a separate table.
- **End of Extended Evaluation Phase Analysis (also corresponds to the final analysis):** This analysis will be conducted once all subjects have completed the Extended Evaluation Phase, including the Follow-up visit, and the database has been locked. All visits and events occurring during the Extended Evaluation Phase will be reported at the end of the study once all subjects have completed the Extended Evaluation Phase.

After the End of Maintenance Phase Analysis, data entered at a visit level will remain locked; data entered in the log pages (e.g. AEs and Concomitant medications) will be unlocked to allow the Investigator to enter additional data (e.g. end date of AEs).

The results generated at the end of the Maintenance Phase are the primary results of the study. The results generated at the end of the Extended Evaluation Phase provide supplementary information.

In the unlikely event that new information that becomes available after the Maintenance Phase database lock potentially impacts locked data, it will be discussed in the final study report.

A Data Review Meeting to determine protocol deviations and analysis populations will be held at the end of the Maintenance Phase. Protocol deviations occurring after the end of the Maintenance Phase will be reported in the End of Extended Evaluation Phase Analysis, but will not lead to exclusion from any of the analysis populations.

Further details regarding the timing of reporting by study phase and the analysis populations are presented in Appendix 15.5.

8.1 *DATA SAFETY MONITORING BOARD*

Safety and limited efficacy data are reviewed by an external, independent DSMB every 6 months, and serious AEs and AESIs are reviewed in near real-time. The primary function of the DSMB is to monitor the study and make recommendations to the Cortendo study team regarding study conduct in order to safeguard the well-being of subjects already in the study and those to be recruited. The DSMB is responsible for providing external oversight and is not involved in the day-to-day conduct of the study. The DSMB will not review efficacy results outside of their mandate to monitor benefits and risks of ongoing study treatment and will not be involved in making recommendations or decisions based primarily on efficacy results (i.e. the DSMB does not advise on futility or early stopping for established efficacy).

No interim analyses of efficacy are planned.

A specific DSMB Charter and an associated SAP provide further details.

9 List of Laboratory Analytes, Units and Precision

Only the following analytes listed in Table 13 will be included in the summary tables, using the units and number of decimal points presented in the below table for the precision level. There is one exception. For HbA1c, the values will be summarized in tables and figures in conventional unit, ie, as %, with 1 decimal point for the precision level. The HbA1c values will be presented in the listings in both conventional and international units.

Table 13: List of Laboratory parameters, units and precision level

Category	Analyte	SI Unit	Decimal point
Biochemistry	Urea Nitrogen	mmol/L	1
Biochemistry	Creatinine	umol/L	1
CS Comorbidity	Glucose	mmol/L	1
Biochemistry	Sodium	mmol/L	0
Biochemistry	Potassium	mmol/L	1
Biochemistry	Chloride	mmol/L	0
Biochemistry	Total CO_2	mmol/L	0
Biochemistry	Calcium	mmol/L	2
Biochemistry	Magnesium	mmol/L	2
Biochemistry	Phosphate	mmol/L	2
Biochemistry	Uric Acid	umol/L	0
Biochemistry	Albumin	g/L	0
Biochemistry	Protein, Total	g/L	0
Biochemistry	AST (SGOT)	U/L	0
Biochemistry	ALT (SGPT)	U/L	0
Biochemistry	GGT	U/L	0
Biochemistry	Alkaline Phosphatase	U/L	0
Biochemistry	Total Bilirubin	umol/L	0
Biochemistry	Direct Bilirubin	umol/L	0
CS Comorbidity	Total Cholesterol	mmol/L	2
CS Comorbidity	LDL-C	mmol/L	2
CS Comorbidity	HDL-C	mmol/L	2
Biochemical Marker	LDL-C:HDL-C	ratio	2
Biochemical Marker	Triglycerides	mmol/L	2

Category	Analyte	SI Unit	Decimal point
Hematology	Platelet count	GI/L	1
Hematology	Red blood cell (RBC)	TI/L	1
Hematology	White blood cell (WBC)	GI/L	1
Hematology	Hemoglobin	g/L	1
Hematology	Hematocrit	1	1
Hematology	MCV	FL	1
Hematology	MCH	pg	1
Hematology	MCHC	g/L	1
Hematology	Abs. Neutrophils *	GI/L	2
Hematology	Abs. Lymphocytes	GI/L	2
Hematology	Abs. Monocytes	GI/L	2
Hematology	Abs. Eosinophils	GI/L	2
Hematology	Abs. Basophils	GI/L	2
Urinalysis	Specific Gravity		3
Urinalysis	pH		1
Biochemical Marker	LNSC	nmol/L	1
Hormone	TSH	mu/L	2
Hormone	Free T4	pmol/L	1
Hormone	FSH	IU/L	1
Biochemical Marker	Albumin/Creatinine Ratio	mg/mmol Creat	1
Urinalysis	Albumin Urine	mg/L	1
Coagulation	INR		1
Coagulation	PT	sec	1
Coagulation	PTT	sec	1
CS Comorbidity	HbA1C	mmol/mol	1

Category	Analyte	SI Unit	Decimal point
OGTT	Glucose, plasma (fasting)	mmol/L	1
Biochemical Marker	Serum Cortisol	nmol/L	2
Biochemical Marker	ACTH	pmol/L	1
Biochemical Marker	CRP	mg/L	1
Hormone	IGF-1	nmol/L	2
Hormone	Testosterone, Total	nmol/L	2
Hormone	Testosterone, Free	nmol/L	2
Hormone	Testosterone, bioavailable	nmol/L	2
Efficacy - Urinalysis	Cortisol, 24-hour	nmol/D	1
Efficacy - Urinalysis	Mean Cortisol, 24-hour	nmol/D	1
Efficacy - Urinalysis	Creatinine Excretion**	mmol/D	1

* Total

** Urine Creatinine

Abbreviations: OGTT = Oral Glucose Tolerance Test.

10 Clarifications and Changes from Planned Analyses in the Protocol

- Primary objective: To clarify, the term “normal UFC” in the primary objective is meant to correspond to mean 24-hour UFC ≤ ULN, which is what is stated in the definition of the primary efficacy endpoint.
- In addition to the 8 CS comorbidities biomarkers that were pre-specified in the protocol, CRP, BMI and abdominal girth are also considered as CS comorbidities biomarkers. It should be noted that change from Baseline in CRP during the Maintenance Phase is already identified as a secondary efficacy endpoint.

- The secondary endpoints section of the protocol amendment 6 (page 34) states 'low and high density lipoproteins' as a CS comorbidity biomarker. This should read 'low and high density lipoprotein-associated cholesterol', therefore in Section 4.1 of this document these endpoints have been correctly defined.
- The secondary endpoints section of the protocol amendment 6 (page 79) states that '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'. The shifts are included but not the t-test, which is not an appropriate test for categorical shifts.
- The exploratory endpoints section of the protocol amendment 6 (page 36) defines the first criterion of clinical benefit as 'Clinical response as indicated by UFC ≤ ULN'. In section 4.1 of this document for clarity this criterion has been defined as 'UFC response as indicated by UFC ≤ ULN'.
- There will be two data locks for this study. For the first data lock, the primary analysis will be performed after the last subject reaches End of Maintenance Phase. For the End-of-Maintenance Phase analyses:
    - Total study exposure will be by study phase, and no summary is planned over the entire study duration.
    - AEs will be summarized up to the End of the Maintenance Phase, and by study phase. No summary is planned over the entire study duration.
    - The protocol references a singular model for CS comorbidity biomarkers. This model is split by Maintenance Phase and Extended Evaluation Phase.
- The terms Clinical Response and Complete or Partial Response were renamed UFC Response and UFC Improvement, respectively, with the following exception. The term Clinical Response is still used to refer to the primary efficacy endpoint.
- Definitions for DT, MC, PK and PD population were added.
- The definition of PP population was modified to require that the subjects complete the Maintenance Phase and that only major protocol deviations that may affect the primary efficacy assessment will be considered.
- Expanded on the DSMB from what is provided in the protocol.
- New section to describe the analysis of Prior Therapy for CS was added.
- Imputation scheme revised to include:
    - Imputation rule added for subjects who withdrew from the study prior to the Maintenance Phase for longitudinal analyses.
    - Creation of a new imputation scheme to assess the impact of a dose increase on UFC response and UFC improvement
- Model methodology: Added region (US vs. non-US) to the longitudinal models, as the study is a multi-center study, and there may be possible regional differences in efficacy.
- Additional statistical testing has been added for CRP
- Exploratory analyses:

  - Two alternative definitions of Clinical Benefit have been added and will be summarized. They are: Clinical Benefit regardless of dose increase and Clinical Benefit with partial UFC normalization.
  - Medication changes are split by study phase.
  - Hypercortisolism / Photograph data were also collected at M3 (D90) visit in addition to Baseline, End of Maintenance Phase visit and End of Extended Evaluation visit; this has been added to the analysis.
- Clarified that safety signals captured at unscheduled visits will be included in shift tables completed at a study phase level.
- New subgroups have been added to those specified in the protocol, as follows:
  - Cushing's Disease
  - Region
  - Age
  - Sex
  - Baseline UFC
  - Baseline LNSC
  - Baseline ACTH
- Clarified CI methodology for the AE analysis and analysis of response rates.
- Included definition of clinically meaningful improvement.
- Added description of graphics to investigate co-medications intake and change in their associated CS comorbidities biomarkers for drugs controlling blood pressure, diabetics and cholesterol.
- Added summary of tumor volume from MRI assessments.
- Added exploratory analysis for intra-subject variability within-visit variability for UFC, LNSC, SBP, DBP and abdominal girth.
- Dexamethasone suppression test (DST) listing is now a screening / disposition listing and not considered as safety data.
- Added exploratory analyses for Diabetes Mellitus, Hypertensive, Hypercholesterolemia, Obesity and Metabolic Syndrom Responders.

11 Tables, Figures And Listing Shells

See separate document for the TFL shells. The TFL shell document will be prepared prior to the dry runs that occurred before the Maintenance Phase database lock. Further changes in the templates may occur after review of the dry runs prior to the Maintenance Phase database lock.

12 Document History

Date	Version	Modified by	Brief details of changes made to template
DDMMMYYYY	1.0	XXXXX	Initial final version.

13 References

[1] 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 Subjects with Cushing's Syndrome. J Clin Endocrinol Metab 2012; 97: 2039-2049.

[2] 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.

[3] 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 subjects with Cushing's disease. Clin Endocrinol. 2013; 0: 1-9.

[4] Hochberg, Y. (1988), A sharper Bonferroni procedure for multiple tests of significance, Biometrika, 75, p 800-803

[5] Hahn, GJ and Meeker WQ. (1991). Statistical Intervals: A Guide for Practitioners, p 82-90. New York: John Wiley & Sons.

14 Appendices

14.1 *PROCEDURE SCHEDULE FOR SCREENING, DOSE TITRATION, MAINTENANCE AND EXTENDED EVALUATION PHASES*

14.1.1 Table 14: Study Flow Chart for Screening, Dose Titration, Maintenance and Extended Evaluation Phases

Assessments	Screening Phase		Dose Titration Phase[1]			Maintenance Phase[2] Months							Extended Eval Phase[3]		FU Visit[4]
	Scrn[5]	Baseline[6]	DL-1	DL-2 DL-3	DL-4 DL-5 DL-6 DL-7	M 1	M 2	M 3	M 4	M 5	M 6	End of MP	M 9	M 12	
Informed Consent	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 Protocol 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)

Assessments	Screening Phase		Dose Titration Phase[1]			Maintenance Phase[2] Months							Extended Eval Phase[3]		FU Visit[4]
	Scrn[5]	Baseline[6]	DL-1	DL-2 DL-3	DL-4 DL-5 DL-6 DL-7	M 1	M 2	M 3	M 4	M 5	M 6	End of MP	M 9	M 12	
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

[6] Baseline procedures should be performed within 14 days (± 7 days) of DL-1 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.

Assessments	Screening Phase		Dose Titration Phase[1]			Maintenance Phase[2] Months							Extended Eval Phase[3]		FU Visit[4]
	Scrn[5]	Baseline[6]	DL-1	DL-2 DL-3	DL-4 DL-5 DL-6 DL-7	M 1	M 2	M 3	M 4	M 5	M 6	End of MP	M 9	M 12	
Assessment of Signs & Symptoms form [9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (BP and HR in triplicate and temperature)	X	X	X	X	X	X	X	X	X	X	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														

[9] Assessment of Clinical Signs & Symptoms form (Protocol 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

Assessments	Screening Phase		Dose Titration Phase[1]			Maintenance Phase[2] Months							Extended Eval Phase[3]		FU Visit[4]
	Scrn[5]	Baseline[6]	DL-1	DL-2 DL-3	DL-4 DL-5 DL-6 DL-7	M 1	M 2	M 3	M 4	M 5	M 6	End of MP	M 9	M 12	
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 evaluations [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			

[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 monthly at each visit 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.

Assessments	Screening Phase		Dose Titration Phase[1]			Maintenance Phase[2] Months							Extended Eval Phase[3]		FU Visit[4]
	Scrn[5]	Baseline[6]	DL-1	DL-2 DL-3	DL-4 DL-5 DL-6 DL-7	M 1	M 2	M 3	M 4	M 5	M 6	End of MP	M 9	M 12	
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
OGTT (pre-diabetics only)		X							X			X	X	X	X

[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

Assessments	Screening Phase		Dose Titration Phase[1]			Maintenance Phase[2] Months							Extended Eval Phase[3]		FU Visit[4]
	Scrn[5]	Baseline[6]	DL-1	DL-2 DL-3	DL-4 DL-5 DL-6 DL-7	M 1	M 2	M 3	M 4	M 5	M 6	End of MP	M 9	M 12	
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

[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

Assessments	Screening Phase		Dose Titration Phase[1]			Maintenance Phase[2] Months							Extended Eval Phase[3]		FU Visit[4]
	Scrn[5]	Baseline[6]	DL-1	DL-2 DL-3	DL-4 DL-5 DL-6 DL-7	M 1	M 2	M 3	M 4	M 5	M 6	End of MP	M 9	M 12	
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
Cushing QoL 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

Assessments	Screening Phase		Dose Titration Phase[1]			Maintenance Phase[2] Months							Extended Eval Phase[3]		FU Visit[4]
	Scrn[5]	Baseline[6]	DL-1	DL-2 DL-3	DL-4 DL-5 DL-6 DL-7	M 1	M 2	M 3	M 4	M 5	M 6	End of MP	M 9	M 12	
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]				

[15] First 24-hour urine collection will be ~Day 10 (±1 day) 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 Protocol Section 6.2.8.1 for details.

14.2 *IDENTIFYING WORST RESULTS FOR LABORATORY PARAMETERS, VITAL SIGNS, ABDOMINAL GIRTH AND ECG PARAMETERS*

Table 15.2.1: Worst results for the laboratory parameters

Category	Analyte	SI Unit	Abnormal result	Worst result
Biochemistry	Urea Nitrogen	mmol/L	Low/high	High
Biochemistry	Creatinine	umol/L	High	High
CS Comorbidity	Glucose	mmol/L	Low/high	Low
Biochemistry	Sodium	mmol/L	Low/high	High
Biochemistry	Potassium	mmol/L	Low/high	Low
Biochemistry	Chloride	mmol/L	Low	Low
Biochemistry	Total CO_2	mmol/L	High	High
Biochemistry	Calcium	mmol/L	Low/high	High
Biochemistry	Magnesium	mmol/L	Low	Low
Biochemistry	Phosphate	mmol/L	Low	Low
Biochemistry	Uric Acid	umol/L	High	High
Biochemistry	Albumin	g/L	Low	Low
Biochemistry	Protein, Total	g/L	Low/high	Low

Category	Analyte	SI Unit	Abnormal result	Worst result
Biochemistry	AST (SGOT)	U/L	High	High
Biochemistry	ALT (SGPT)	U/L	High	High
Biochemistry	GGT	U/L	High	High
Biochemistry	Alkaline Phosphatase	U/L	High	High
Biochemistry	Total Bilirubin	umol/L	High	High
Biochemistry	Direct Bilirubin	umol/L	High	High
CS Comorbidity	Total Cholesterol	mmol/L	High	High
CS Comorbidity	LDL-C	mmol/L	High	High
CS Comorbidity	HDL-C	mmol/L	Low	Low
Biochemical Marker	LDL-C:HDL-C	ratio	High	High
Biochemical Marker	Triglycerides	mmol/L	High	High
Hematology	Platelet count	GI/L	Low/high	Low
Hematology	Red blood cell (RBC)	TI/L	Low/high	Low
Hematology	White blood cell (WBC)	GI/L	Low/high	Low
Hematology	Hemoglobin	g/L	Low/high	Low
Hematology	Hematocrit	1	Low/high	Low
Hematology	MCV	FL	Low/high	Low

Category	Analyte	SI Unit	Abnormal result	Worst result
Hematology	MCH	pg	Low	Low
Hematology	MCHC	g/L	Low/high	Low
Hematology	Abs. Neutrophils *	GI/L	Low/high	Low
Hematology	Abs. Lymphocytes	GI/L	Low/high	High
Hematology	Abs. Monocytes	GI/L	High	High
Hematology	Abs. Eosinophils	GI/L	High	High
Hematology	Abs. Basophils	GI/L	High	High
Urinalysis	Specific Gravity		Low/high	Low
Urinalysis	pH		Low/high	Low
Biochemical Marker	LNSC	nmol/L	Low	Low
Hormone	TSH	mu/L	Low/high	Low
Hormone	Free T4	pmol/L	Low/high	High
Hormone	FSH	IU/L	Low/high	High
Biochemical Marker	Albumin/Creatinine Ratio	mg/mmol Creat	Low/high	High
Urinalysis	Albumin Urine	mg/L	High	High
Coagulation	INR		High	High

Category	Analyte	SI Unit	Abnormal result	Worst result
Coagulation	PT	sec	High	High
Coagulation	PTT	sec	High	High
CS Comorbidity	HbA1C	mmol/mol	High	High
OGTT	Glucose, plasma (fasting)	mmol/L	High	High
Biochemical Marker	Serum Cortisol	nmol/L	Low/high	Low
Biochemical Marker	ACTH	pmol/L	Low/high	High
Biochemical Marker	CRP	mg/L	High	High
Hormone	IGF-1	nmol/L	High	High
Hormone	Testosterone, Total	nmol/L	Low	Low
Hormone	Testosterone, Free	nmol/L	Low	Low
Hormone	Testosterone, bioavailable	nmol/L	Low	Low
* Total Abbreviations: OGTT = Oral Glucose Tolerance Test.				

Table 15.2.2: Worst results for the vital signs and abdominal girth

Parameter	SI Unit	Abnormal result	Worst result
SBP	mmHg	Low/high	High
DBP	mmHg	Low/high	High
BMI	kg/m^2	Low/high	High
Weight	kg	Low/high	High
Abdominal girth	cm	Low/high	High

Table 15.2.3: Worst results for the ECG parameters

Parameter	SI Unit	Abnormal result	Worst result
Heart Rate	bpm	Low/high	Low
QT Interval	msec	High	High
QT Duration	msec	High	High
QTcB	msec	High	High
QTcF	msec	High	High
QRS Complex	msec	High	High

Parameter	SI Unit	Abnormal result	Worst result
QRS Duration	msec	High	High
QRS Axis	deg	High	High
PR Interval	msec	Low/high	Low
RR Interval	msec	Low/high	Low
RR Duration	msec	Low/high	Low

14.3 *VISIT WINDOWS*

Table 16: Visit Windows

Study Phase	Period	Repeat#	Relative Day	Relative day from:	Efficacy Visit Window (exclude vital signs, and MRI)	Safety Visit Window (include vital signs, and MRI)
Baseline	Screening/ Baseline		1	First dose	[-14; -1]	
Dose Titration Phase*	DL1	1	1	First dose	Any data collected under DL1, repeat 1	
	DL2	1	1	First dose at DL2 (first time)	Any data collected under DL2, repeat 1	
	DL3	1	1	First dose at DL3 (first time)	Any data collected under DL3, repeat 1	

Study Phase	Period	Repeat#	Relative Day	Relative day from:	Efficacy Visit Window (exclude vital signs, and MRI)	Safety Visit Window (include vital signs, and MRI)
	DL4 – D1	1	1	First dose at DL4 (first time)	Any data collected under DL4 –D1, repeat 1	
	DL4 – D4-7	1	5	First dose at DL4 (first time)	Any data collected under DL4 – D4-7, repeat 1	
	DL4- D14-16	1	15	First dose at DL4 (first time)	Any data collected under DL4 – D14 -16, repeat 1	
	(cont.)					
	DL3	2	1	First dose at DL3 (second time)	Any data collected under DL3, repeat 2	
	DL4 – D1	2	1	First dose at DL4 (second time)	Any data collected under DL4 – D1, repeat 2	
	(cont.)					
Maintenance Phase**	Month 1		1	First dose in Maintenance Phase	UFC: Not Applicable LNSC: [-10, 14] Other parameters: [1;14]	[1; 14]
	Month 2		30	First dose in Maintenance Phase	[15; 49]	[15; 49]

Study Phase	Period	Repeat#	Relative Day	Relative day from:	Efficacy Visit Window (exclude vital signs, and MRI)	Safety Visit Window (include vital signs, and MRI)
	Month 3		60	First dose in Maintenance Phase	[50; 79]	[50; 79]
	Month 4		90	First dose in Maintenance Phase	[80; 109]	[80; 109]
	Month 5		120	First dose in Maintenance Phase	[110; 139]	[110; 139]
	Month 6		150	First dose in Maintenance Phase	[140; 169]	[140; 169]
	End of Maintenance Phase		180	First dose in Maintenance Phase	[170; 200]	[170; 200]
Extended Evaluation Phase**	Month 9		270	First day post Maintenance Phase	[201; 315]	[201; 315]
	Month 12		360	First day post Maintenance Phase	[316; 400]	[316; 400]
Follow-up			14	From last dose date	[1, 35]	[1, 35]

Study Phase	Period	Repeat#	Relative Day	Relative day from:	Efficacy Visit Window (exclude vital signs, and MRI)	Safety Visit Window (include vital signs, and MRI)

* Study drug interruptions will be ignored when assigning a result in the Dose Titration Phase to the appropriate dose level.

** If the subject discontinued early or was irradiated, data collected strictly post last dose, will be summarized / analyzed under Follow-up visit.

Note: For ECGs, if for a given date for a subject, there are both a centrally read ECG from Spaulding and a local ECG on that same day, the ECG from Spaulding will be the one included when applying the visit windows.

14.4 *BDI-II SCORING INFORMATION*

Question Response		Answer Score	Question Score
1.	Sadness		
	I do feel sad.	0	
	I feel sad much of the time.	1	
	I am sad all the time.	2	
	I am so sad or unhappy that I can't stand it.	3	
2.	Pessimism		
	I am not discouraged about my future.	0	
	I feel more discouraged about my future than I used to be.	1	
	I do not expect things to work out for me.	2	
	I feel my future is hopeless and will only get worse.	3	
3.	Past Failure		
	I do not feel like a failure.	0	
	I have failed more than I should have.	1	
	As I look back, I see a lot of failures.	2	
	I feel I am a total failure as a person.	3	
4.	Loss of Pleasure		
	I get as much pleasure as I ever did from the things I enjoy.	0	
	I don't enjoy things as much as I used to.	1	
	I get very little pleasure from the things I used to enjoy.	2	
	I can't get any pleasure from the things I used to enjoy.	3	
5.	Guilty Feelings		
	I don't feel particularly guilty.	0	
	I feel guilty over many things I have done or should have done.	1	
	I feel quite guilty most of the time.	2	
	I feel guilty all of the time.	3	

Question Response	Answer Score	Question Score
6. Punishment Feelings		
I don't feel I am being punished.	0	
I feel I may be punished.	1	
I expect to be punished.	2	
I feel I am being punished.	3	
7. Self-Dislike		
I feel the same about myself as ever.	0	
I have lost confidence in myself.	1	
I am disappointed in myself.	2	
I dislike myself.	3	
8. Self-Criticalness		
I don't criticize or blame myself more than usual.	0	
I am more critical of myself than I used to be.	1	
I criticize myself for all my faults.	2	
I blame myself for everything bad that happens.	3	
9. Suicidal Thoughts or Wishes		
I don't have any thoughts of killing myself.	0	
I have thoughts of killing myself, but I would not carry them out.	1	
I would like to kill myself.	2	
I would kill myself if I had the chance.	3	
10. Crying		
I don't cry any more than I used to.	0	
I cry more than I used to.	1	
I cry over every little thing.	2	
I feel like crying, but I can't.	3	

Question Response	Answer Score	Question Score
11. Agitation		
I am no more restless or wound up than usual.	0	
I feel more restless or wound up than usual.	1	
I am so restless or agitated that it's hard to stay still.	2	
I am so restless or agitated that I have to keep moving or doing something.	3	
12. Loss of Interest		
I have not lost interest in other people or activities.	0	
I am less interested in other people or things than before.	1	
I have lost most of my interest in other people or things.	2	
It's hard to get interested in anything.	3	
13. Indecisiveness		
I make decisions about as well as ever.	0	
I find it more difficult to make decisions than usual.	1	
I have much greater difficulty in making decisions than I used to.	2	
I have trouble making any decision.	3	
14. Worthlessness		
I do not feel I am worthless.	0	
I don't consider myself as worthwhile and useful as I used to.	1	
I feel more worthless as compared to other people.	2	
I feel utterly worthless.	3	
15. Loss of Energy		
I have as much energy as ever.	0	
I have less energy than I used to have.	1	
I don't have enough energy to do very much.	2	
I don't have enough energy to do anything.	3	

Question Response	Answer Score	Question Score
16. Changes in Sleeping Pattern		
I have not experienced any change in my sleeping pattern.	0	
I sleep somewhat more than usual.	1	
I sleep somewhat less than usual.	1	
I sleep a lot more than usual.	2	
I sleep a lot less than usual.	2	
I sleep most of the day.	3	
I wake up 1–2 hours early and can't get back to sleep.	3	_____
17. Irritability		
I am no more irritable than usual.	0	
I am more irritable than usual.	1	
I am much more irritable than usual.	2	
I am irritable all the time.	3	_____
18. Changes in Appetite		
I have not experienced any change in my appetite.	0	
My appetite is somewhat less than usual.	1	
My appetite is somewhat greater than usual.	1	
My appetite is much less than before.	2	
My appetite is much greater than usual.	2	
I have no appetite at all.	3	
I crave food all the time.	3	_____
19. Concentration Difficulty		
I can concentrate as well as ever.	0	
I can't concentrate as well as usual.	1	
It's hard to keep my mind on anything for very long.	2	
I find I can't concentrated on anything.	3	_____

Question Response		Answer Score	Question Score
20.	Tiredness or Fatigue		
	I am no more tired or fatigued than usual.	0	
	I get more tired or fatigued more easily than usual.	1	
	I am too tired or fatigued to do a lot of the things I used to do.	2	
	I am too tired or fatigued to do most of the things I used to do.	3	
21	Loss of Interest in Sex		
	I have not noticed any recent change in my interest in sex.	0	
	I am less interested in sex than I used to be.	1	
	I am much less interested in sex now.	2	
	I have lost interest in sex completely.	3	
	TOTAL SCORE (Sum of all responses)		

14.5 *STUDY ENDPOINTS BY POPULATION, PHASE AND TIMING OF ANALYSIS*

Table 17: Study endpoints by population, phase and timing of analysis

	Analysis Set						Maintenance Phase Database Lock				End of Study Database Lock
	All	ITT	DT	M	MC	PP	Baseline	Dose Titration Phase	Maintenance Phase	Extended Evaluation Phase	Extended Evaluation Phase
Supportive Data											
Subject Disposition	x	x					x	x	x		x
Summary of Populations	x						x				
Demographic and Baseline		x	x	x	x	x	x				
Protocol Deviations Leading to Exclusion from the PP Population		x									
Medical History		x	x		x						
Disease Characteristics		x	x		x		x				
Other Medical History		x			x		x				
Prior Medications		x					x				
New and Continuing Medications		x					x	x	x		x

	Analysis Set						Maintenance Phase Database Lock				End of Study Database Lock
	All	ITT	DT	M	MC	PP	Baseline	Dose Titration Phase	Maintenance Phase	Extended Evaluation Phase	Extended Evaluation Phase
Prior CS Drug Therapy, Radiotherapy and Surgery		x					x				
Study Drug Exposure and Compliance		x			x	x		x	x		x
Primary Endpoint											
Primary Analysis of UFC Response		x		x	x	x			x		
Secondary Endpoints											
Other analyses of UFC Response and/or Improvement		x		x	x	x		x	x		x
Summaries and Plots of UFC Response and/or Improvement by Visit (and/or Dose, if applicable)		x	x*	x*	x	x*		x	x		
Individual Plots of Change from Baseline to End of Maintenance Phase in UFC					x				x		

	Analysis Set						Maintenance Phase Database Lock				End of Study Database Lock
	All	ITT	DT	M	MC	PP	Baseline	Dose Titration Phase	Maintenance Phase	Extended Evaluation Phase	Extended Evaluation Phase
Plots of Effect of Dose Increases During the Maintenance Phase of UFC					x						
Serum and LNSC		x			x			x	x		x
CS Comorbidities Biomarkers		x			x			x	x		x
Clinical signs and symptoms of CS		x			x			x	x		
Cushing Quality of Life Total Score		x			x			x	x		x
BDI-II Total Score		x			x			x	x		x
OGTT and Spot Albumin/Creatinine Ratio		x			x			x	x		x
Abnormal Spot Albumin/Creatinine Ratio		x						x	x		x
Exploratory Endpoints											
Clinical Benefit Rate		x							x		x
Changes to Antihypertensive, Anti-diabetic, Cholesterol-lowering Medications		x							x		x
Hypercortisolism from Photographs Scores		x							x		x

	Analysis Set						Maintenance Phase Database Lock				End of Study Database Lock
	All	ITT	DT	M	MC	PP	Baseline	Dose Titration Phase	Maintenance Phase	Extended Evaluation Phase	Extended Evaluation Phase
Intra-subject Within Visit Variability for Applicable Efficacy Parameters		x							x		x
Other Exploratory Analysis											
Diabetes Mellitus Responders		x							x		
Hypertension Responders		x							x		
Hypercholesterolemia Responders		x							x		
Obesity Responders		x							x		
Safety Endpoints											
AEs		x	x^					x	x	x	x
Clinical Laboratory Assessments (changes from baseline)		x									
Clinical Laboratory Assessments (summary statistics, shift tables, plots)		x	x^					x	x		x

	Analysis Set						Maintenance Phase Database Lock				End of Study Database Lock
	All	ITT	DT	M	MC	PP	Baseline	Dose Titration Phase	Maintenance Phase	Extended Evaluation Phase	Extended Evaluation Phase
Hormones and Biomarkers Laboratory Evaluations		x						x	x		x
ACTH		x	x		x			x	x		
Vital Signs		x						x	x		x
ECG Parameters		x	x^					x	x		x
Tumor size and volume		x						x	x		x

* Selected summaries only, see Section 8.8 for further details.

^ Selected Summaries only, see Section 8.11 for further details.