Title: Phase 2 Study of the Safety and Efficacy of CORT125134 in the Treatment of Endogenous Cushing's Syndrome

NCT number: NCT02804750

Date: 30 August 2018

STATISTICAL ANALYSIS PLAN

Corcept Therapeutics

CORT125134-451

Protocol Title:	Phase 2 Study of the Safety and Efficacy of CORT125134 in the Treatment of Endogenous Cushing's Syndrome
Protocol Version and Date:	Version 7.0; 15 January 2018
Sponsor:	Corcept Therapeutics 149 Commonwealth Drive Menlo Park, California 94025 US
Prepared By:	[redacted]
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1 STATISTICAL ANALYSIS PLAN APPROVAL

Sponsor:	Corcept Therapeutics
Clinical Protocol Number:	CORT125134-451
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3 LIST OF ABBREVIATIONS

Table 1 List of Abbreviations

Abbreviation	Definition
ACTH	adrenocorticotropic hormone
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
BDI-II	Beck Depression Inventory
BMI	body mass index
BP	blood pressure
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DHEA-S	dehydroepiandrosterone sulfate
DRC	data review committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ET	Early Termination
GR	glucocorticoid reception
HbA1c	glycated hemoglobin
HEENT	head, eyes, ears, nose, throat
HOMA-IR	homeostatic model assessment for insulin resistence
HPA	hypothalamic-pituitary-adrenal
HT	hypertension
ICH	International Conference on Harmonization
IGF	insulin-like growth factor
IGT	impaired glucose tolerance/diabetes
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
mPP	Modified Per-Protocol
mRNA	messenger ribonucleic acid
NTx	N-telopeptides of type 1 collagen
oGTT	oral glucose tolerance test

Abbreviation	Definition
PK	pharmacokinetic
QC	quality control
REML	restricted maximum likelihood
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SI	Système International
T3	triiodothyronine
T4	thyroxine
TEAE	treatment-emergent adverse event
UFC	urinary free cortisol
WBC	white blood cell
WHO	World Health Organization

4 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide comprehensive and detailed descriptions of the methods and presentation of data analyses proposed for Corcept Therapeutics Protocol CORT125134-451 (Phase 2 Study of the Safety and Efficacy of CORT125134 in the Treatment of Endogenous Cushing's Syndrome). Descriptions of planned analyses are provided in order to avoid post hoc decisions that may affect the interpretation of the statistical analysis. The statistical methods applied in the design and planned analyses of this study are consistent with the International Conference on Harmonisation (ICH) guideline *Statistical Principles for Clinical Trials* (E9) (1998).

The clinical study database will be locked following a review of all data in the database and resolution of all data queries. This SAP will be finalized prior to data analysis and before database lock to provide full details, including templates for tables, listings, and figures, to be presented in the clinical study report (CSR). Any changes between the statistical methods provided in the clinical study protocol and this SAP will be explained herein; any changes or deviations from this SAP relative to the final analysis will be fully documented in the CSR. Minor changes or deviations from the templates for tables, figures, and listings need not be documented in the CSR.

5 STUDY OBJECTIVES

5.1 Primary Study Objective

The primary objective of this study is to assess the safety of CORT125134 in patients with endogenous Cushing syndrome.

5.2 Secondary Study Objective

The secondary objective of this study is to assess the evidence of reduction in cortisol activity following treatment with CORT125134 in patients with endogenous Cushing syndrome, based on improvement in blood glucose control and/or blood pressure (BP).

6 INVESTIGATIONAL PLAN

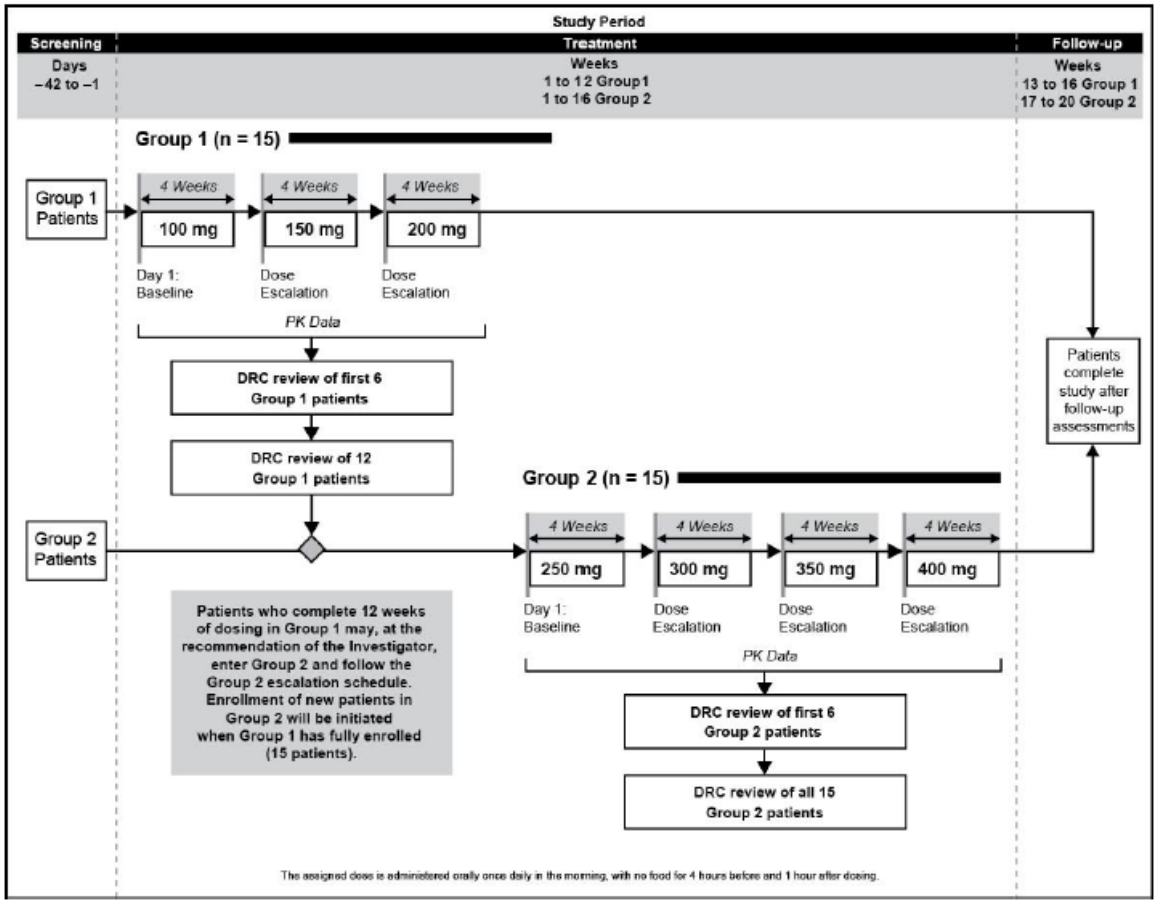
6.1 Overall Study Design

This is a Phase 2, open-label study to evaluate the safety and efficacy of two dose regimens of CORT125134 (also known as relacorilant) in patients with endogenous Cushing syndrome and type 2 diabetes or glucose intolerance and/or uncontrolled or untreated hypertension. Patients will be categorized in the impaired glucose tolerance/diabetes subgroup or the hypertension subgroup; a patient may be in both of these subgroups.

Approximately 30 patients will be enrolled across clinical sites in the United States and Europe. As shown in Figure 1, two dose groups (Groups 1 and 2), including 15 patients

per group, will be evaluated. The study will consist of a screening period (Days −42 to −1); 4-week treatment periods that start with the initial dose and immediately escalate to the next higher dose every 4 weeks; and a follow-up period of 4 weeks. Full steady-state pharmacokinetic (PK) profiles will be generated at every dose level as noted in Section 6.2.

Figure 1 Study Design



All patients will undergo at least a two-step dose escalation (Figure 1). Patient dosing will be done at home, except on days of study visits.

For Group 1, patient visits to the study site will be at screening, on Day 1 (baseline), Weeks 2, 4, 6, 8, 10, and 12, and after a 4-week follow-up period. For Group 2, patient visits to the study site will be at Day 1 (baseline), Weeks 2, 4, 6, 8, 10, 12, 14, 16, and after a 4-week follow-up period.

The following safety assessments will be performed during each in-clinic visit: adverse event (AE) reporting, safety laboratory tests, physical examinations, vital sign measurements, electrocardiograms (ECGs), concomitant medication reviews, and pregnancy tests. Key efficacy parameters will also be measured, including effects on glucose tolerance, blood pressure, cortisol concentration, body/weight composition, and metabolism.

An independent data review committee (DRC) will convene at least four times to review safety and PK results. The details of the DRC meeting schedule are described in the DRC charter. The results of the assessments and recommendations regarding dose escalation are documented in the DRC meeting minutes.

While the study protocol allows for the possibility of the patients from Group 1 to roll over into Group 2, no patients rolled over from Group 1 to Group 2. Therefore, all analyses will treat Group 1 and Group 2 as mutually exclusive analysis sets.

6.2 Pharmacokinetic Assessments

Predose and postdose samples for serial PK will be collected at Weeks 2, 6, and 10. Predose trough PK samples only will be collected at Weeks 4, 8, and 12/early termination (ET) for patients in Group 1 and Group 2.

For patients in Group 2 who dose-escalate to 400 mg daily, predose and postdose samples for serial PK will also be collected at Week 14, and key efficacy parameters as well as predose trough PK samples will be collected at Week 16/ET.

Between clinic visits, weekly contact with patients will occur via email or telephone to capture study drug compliance, AEs, and medication changes.

Methods for analysis of PK data are described in a separate PK analysis plan.

6.3 Schedule of Events for Group 1

Assessment/Procedure		Treatment Period													
Visit Name	Screening	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12/ Early Term [a]	Week 16 Follow-Up [b]
Day Number/ Window	Day −42 to Day −1	Day 1	Day 7±1	Day 14±2	Day 21±1	Day 28±2	Day 35±1	Day 42±2	Day 49±1	Day 56±2	Day 63±1	Day 70±2	Day 77±1	Day 84±2	Day 112+7
Informed consent	X														
Medication washout [c]	X														
Demographics and baseline disease characteristics	X														
Medical history, medication history [d]	X														
Height	X														
Inclusion/exclusion criteria	X	X													
Enrollment		X													
Dexamethasone suppression test	X [e]														
Study drug dispensing		X		X		X		X		X		X			
Study drug compliance			X	X	X	X	X	X	X	X	X	X	X	X	
Patient diary		X		X		X		X		X		X		X	
Efficacy Assessments															
Body weight	X	X		X		X		X		X		X		X	X
Waist circumference		X				X				X				X	X
24-hour UFC with creatinine (Ca, Na collection) [f]	X [c, g]			X		X		X		X		X		X	
Salivary cortisol [f]	X [c, h]			X		X		X		X		X		X	
2-hour oGTT [i]	X [c]	X				X				X				X	
24-hour ambulatory BP test	X [c, j]			X		X		X		X		X		X	
HbA1c	X [k]	X												X	
Fructosamine		X		X		X		X		X		X		X	
Adiponectin		X				X				X				X	
Lipid panel [l]		X				X				X				X	X
Sit-to-stand test		X				X				X				X	

Assessment/Procedure		Treatment Period													
Visit Name	Screening	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12/ Early Term [a]	Week 16 Follow-Up [b]
Day Number/ Window	Day −42 to Day −1	Day 1	Day 7±1	Day 14±2	Day 21±1	Day 28±2	Day 35±1	Day 42±2	Day 49±1	Day 56±2	Day 63±1	Day 70±2	Day 77±1	Day 84±2	Day 112+7
Menstrual cycle information [m]	X	X		X		X		X		X		X		X	
Sex hormone levels [n]		X												X	
Coagulation panel [o]		X				X				X				X	
GR activity biomarkers test		X				X				X				X	
Bone laboratory parameters [p]		X				X				X				X	
HPA axis tests [q]	X	X		X		X		X		X		X		X	
ACTH precursors		X		X		X		X		X		X		X	
High sensitivity C-reactive protein		X				X				X				X	
IGF-1		X				X				X				X	
Thyroid tests [r]	X	X		X		X		X		X		X		X	
Trail making test		X				X				X				X	
CushingQoL questionnaire		X				X				X				X	X
BDI-II questionnaire		X				X				X				X	
Physician's Global Assessment		X		X		X		X		X		X		X	X
Pharmacokinetic Assessments															
PK serial blood samples [s]				X				X				X			
PK trough [s]						X				X				X	
Safety Assessments															
Complete physical examination	X	X		X		X		X		X		X		X	X
Vital signs [t]	X	X		X		X		X		X		X		X	X
Electrocardiogram, 12-lead (2 h ±30 min after study drug dosing) [u]	X			X		X		X		X		X		X	X
Pregnancy test [v]	X	X		X		X		X		X		X		X	X
Chemistry and hematology [w]	X	X		X		X		X		X		X		X	X
Adverse event monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

ACTH = adrenal corticotropic hormone; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; BDI-II = Beck Depression Inventory; Ca = calcium; DHEA-S = dehydroepiandrosterone sulfate; EAS = ectopic ACTH secretion; ET = early termination; HbA1c = glycated hemoglobin; IGF = insulin-like growth factor; oGTT = oral glucose tolerance test; Na = sodium; RBC = red blood cell; T3 = triiodothyronine; T4 = thyroxine; UFC = urinary free cortisol; WBC = white blood cell

Note: Collect pituitary MRI radiographic scans and assessments in patients with Cushing disease that are obtained up to 6 months before Day 1 and up to 1 month after last CORT125134 dose if they are available.

a For patients rolling over from Group 1 to Group 2, the Group 1 Week 12 visit will serve as the baseline visit for their Group 2 treatment period.

b This visit is not necessary for patients who roll over from Group 1 to Group 2.

c Medications used in the treatment of Cushing syndrome are prohibited and require washout (as applicable) during screening provided the intervals specified in Exclusion Criterion fit within the screening window. Patients requiring washout of a medication for Cushing syndrome must complete the screening/baseline 24-hour UFC tests, salivary cortisol tests, oGTTs, and 24-hour ambulatory BP monitoring tests after washout and within 3 weeks before Day 1 dosing.

d Medication history only for medications taken to treat Cushing syndrome, hypertension, or diabetes within 3 months before screening.

e Dexamethasone suppression test only if needed for study entry.

f Within 7 days before the Week 2, 4, 6, 8, 10, and 12 visits, samples will be collected by the patient at home twice for each time point.

g The 24-hour UFC will be collected by the patient at home at least two times and up to four times during screening. For screening, the average of the results will serve as “baseline”.

h Salivary cortisol test will be performed by the patient at home at least two and up to four times on different nights during screening. The average of the results will serve as “baseline”.

i oGTTs during the Treatment Period (including on Day 1) will be performed in the impaired glucose tolerance/diabetes subgroup only. During the 2-hour oGTT, blood samples for plasma glucose and insulin will be collected before the glucose drink and 0.5, 1, 1.5, and 2 hours after the glucose drink.

j The 24-hour ambulatory BP will be assessed for all patients during the screening period. For the subgroup of patients who qualify for the hypertension subgroup, there must be a 24-hour ambulatory BP test done within 3 weeks before Day 1; this result will be used as “baseline”. If the initial screening test was done within 3 weeks before Day 1, it does not need to be repeated. Ambulatory BP measurements during the Treatment Period will be performed in the hypertension subgroup only.

k Not required to be collected at screening if results available within 3 months of first dose of study drug at baseline/Day 1.

l Total cholesterol, low-density lipoproteincholesterol, high-density -lipoproteincholesterol-, very low-density lipoprotein-cholesterol, and triglycerides.

m Only in premenopausal female patients not taking hormonal birth control.

n Estradiol, total and free testosterone, sex hormone binding globulin, follicle-stimulating hormone, and luteinizing hormone.

o Activated partial thromboplastin time, Factor VIII, Factor IX, Factor X, and von Willebrand factor, d-dimer, fibrinogen, and thrombinantithrombin-.

p Blood: osteocalcin, bone alkaline phosphatase; urine: N-telopeptides of type 1 collagen.

q Blood samples for analysis of plasma ACTH, serum cortisol, 17-OH-progesterone, 11-deoxycortisol, DHEA-S, and androstenedione.

r Thyroid function tests will include the following: free T4, free T3, reverse T3, thyroid-stimulating hormone.

s Blood levels of CORT125134 and metabolites will be measured predose and at 1, 2, 4, 6, and 8 hours postdose at Weeks 2, 6, and 10 and predose only at Weeks 4, 8, and 12/ET.

t BP, heart rate, respiratory rate, oral body temperature.

u Triplicate ECGs at screening; duplicate ECGs at other study visits.

v Screening blood pregnancy test; all subsequent tests are urine tests.

w Chemistry parameters will include a full chemistry profile (albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen, calcium, chloride, cholesterol, creatinine, glucose, lactate dehydrogenase, magnesium, phosphorus, potassium, sodium, total creatine kinase, total and direct bilirubin, total protein, uric acid). Hematology parameters will include a complete blood count (hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin volume, mean corpuscular volume, mean platelet volume, platelet count, red blood cell distribution width, RBC count, and WBC count) and differential (percent and absolute for the following: basophils, eosinophils, lymphocytes, monocytes, and neutrophils).

6.4 Schedule of Events for Group 2

Assessment/Procedure		Treatment Period															
Visit Name	Screening [a]	Baseline [b]	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Weeks 11, 13, 15	Week 12	Week 14	Week 16/ Early Term	Week 20 Follow-Up
Day Number/ Window	Day −42 to Day −1	Day 1	Day 7±1	Day 14±2	Day 21±1	Day 28±2	Day 35±1	Day 42±2	Day 49±1	Day 56±2	Day 63±1	Day 70±2	Days 77, 91, 105±1	Day 84±2	Day 98±2	Day 112±2	Day 140+7
Informed consent	X																
Medication washout [c]	X																
Demographics and baseline disease characteristics	X																
Medical history, medication history [d]	X																
Height	X																
Inclusion/exclusion criteria	X	X															
Enrollment		X															
Dexamethasone suppression test	X [e]																
Study drug dispensing		X		X		X		X		X		X		X	X		
Study drug compliance			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Patient diary		X		X		X		X		X		X		X	X	X	
Efficacy Assessments																	
Body weight	X	X		X		X		X		X		X		X	X	X	X
Waist circumference		X				X				X				X		X	X
24-hour UFC with creatinine (Ca, Na collection) [f]	X [c,g]			X		X		X		X		X		X	X	X	
Salivary cortisol [f]	X [c,h]			X		X		X		X		X		X	X	X	
2-hour oGTT [i]	X [c]	X				X				X				X		X	
24-hour ambulatory BP test	X [c,j]			X		X		X		X		X		X	X	X	
HbA1c	X [k]	X												X		X	
Fructosamine		X		X		X		X		X		X		X	X	X	
Adiponectin		X				X				X				X		X	
Lipid panel [l]		X				X				X				X		X	X
Sit-to-stand test		X				X				X				X		X	
Menstrual cycle information [m]	X	X		X		X		X		X		X		X	X	X	
Sex hormone levels [n]		X														X	
Coagulation panel [o]		X				X				X				X		X	
GR activity biomarkers test		X				X				X				X		X	

Assessment/Procedure		Treatment Period															
Visit Name	Screening [a]	Baseline [b]	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Weeks 11, 13, 15	Week 12	Week 14	Week 16/ Early Term	Week 20 Follow-Up
Day Number/ Window	Day −42 to Day −1	Day 1	Day 7±1	Day 14±2	Day 21±1	Day 28±2	Day 35±1	Day 42±2	Day 49±1	Day 56±2	Day 63±1	Day 70±2	Days 77, 91, 105±1	Day 84±2	Day 98±2	Day 112±2	Day 140+7
Bone laboratory parameters [p]		X				X				X				X		X	
HPA axis tests [q]	X	X		X		X		X		X		X		X	X	X	
ACTH precursors		X		X		X		X		X		X		X	X	X	
High sensitivity Creactive- protein		X				X				X				X		X	
IGF-1		X				X				X				X		X	
Thyroid tests [r]	X	X		X		X		X		X		X		X	X	X	
Trail making test		X				X				X				X		X	
CushingQoL questionnaire		X				X				X				X		X	X
BDI-II questionnaire		X				X				X				X		X	
Physician's Global Assessment		X		X		X		X		X		X		X	X	X	X
Pharmacokinetic Assessments																	
PK serial blood samples [s]				X				X				X			X		
PK trough [s]						X				X				X		X	
Safety Assessments																	
Complete physical examination	X	X		X		X		X		X		X		X	X	X	X
Vital signs [t]	X	X		X		X		X		X		X		X	X	X	X
Electrocardiogram, 12-lead (2 h ±30 min after study drug dosing) [u]	X			X		X		X		X		X		X	X	X	X
Pregnancy test [v]	X	X		X		X		X		X		X		X	X	X	X
Chemistry and hematology [w]	X	X		X		X		X		X		X		X	X	X	X
Adverse event monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

ACTH = adrenal corticotropic hormone; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; BDI-II = Beck Depression Inventory; Ca = calcium; DHEA-S = dehydroepiandrosterone sulfate; EAS = ectopic ACTH secretion; ET = early termination; HbA1c = glycated hemoglobin; IGF = insulin-like growth factor; oGTT = oral glucose tolerance test; Na = sodium; RBC = red blood cell; T3 = triiodothyronine; T4 = thyroxine; UFC = urinary free cortisol; WBC = white blood cell

Note: Collect pituitary MRI radiographic scans and assessments in patients with Cushing disease that are obtained up to 6 months before Day 1 and up to 1 month after last CORT125134 dose if they are available.

a This visit is not necessary for patients rolling from Group 1 to Group 2.

b For patients rolling over from Group 1 to Group 2, the Group 1 Week 12 visit will serve as the baseline visit for their Group 2 treatment period.

c Medications used in the treatment of Cushing syndrome are prohibited and require washout (as applicable) during screening provided the intervals specified in Exclusion Criterion fit within the screening window. Patients requiring washout of a medication for Cushing syndrome must complete the screening/baseline 24-hour UFC tests, salivary cortisol tests, oGTTs, and 24-hour ambulatory BP monitoring tests after washout and within 3 weeks before Day 1 dosing.

d Medication history only for medications taken to treat Cushing syndrome, hypertension, or diabetes within 3 months before screening.

e Dexamethasone suppression test only if needed for study entry.

f The Week 2, 4, 6, 8, 10, 12, 14, and 16 samples will be collected by the patient at home twice for each time point.

g The 24-hour UFC will be collected by the patient at home at least two times and up to four times during screening. For screening, the average of the results will serve as “baseline”.

h Salivary cortisol test will be performed by the patient at home at least two and up to four times on different nights during screening. The average of the results will serve as “baseline”.

i oGTTs during the Treatment Period (including on Day 1) will be performed in the impaired glucose tolerance/diabetes subgroup only. During the 2-hour oGTT, blood samples for plasma glucose and insulin will be collected before the glucose drink and 0.5, 1, 1.5, and 2 hours after the glucose drink.

j The 24-hour ambulatory BP will be assessed for all patients during the screening period. For the subgroup of patients who qualify for the hypertension subgroup, there must be a 24-hour ambulatory BP test done within 3 weeks before Day 1; this result will be used as “baseline”. If the initial screening test was done within 3 weeks before Day 1, it does not need to be repeated. Ambulatory BP measurements during the Treatment Period will be performed in the hypertension subgroup only.

k Not required to be collected at screening if results available within 3 months of first dose of study drug at baseline/Day 1.

l Total cholesterol, low-density lipoproteincholesterol, high-density -lipoproteincholesterol-, very low-density lipoprotein-cholesterol, and triglycerides.

m Only in premenopausal female patients not taking hormonal birth control.

n Estradiol, total and free testosterone, sex hormone binding globulin, follicle-stimulating hormone, and luteinizing hormone.

o Activated partial thromboplastin time, Factor VIII, Factor IX, Factor X, and von Willebrand factor, d-dimer, fibrinogen, and thrombinantithrombin-.

p Blood: osteocalcin, bone alkaline phosphatase; urine: N-telopeptides of type 1 collagen.

q Blood samples for analysis of plasma ACTH, serum cortisol, 17-OH-progesterone, 11-deoxycortisol, DHEA-S, and androstenedione.

r Thyroid function tests will include the following: free T4, free T3, reverse T3, thyroid-stimulating hormone.

s Blood levels of CORT125134 and metabolites will be measured predose and at 1, 2, 4, 6, and 8 hours postdose at Weeks 2, 6, 10, and 14 and predose only at Weeks 4, 8, 12, and 16/ET.

t BP, heart rate, respiratory rate, oral body temperature.

u Triplicate ECGs at screening; duplicate ECGs at other study visits.

v Screening blood pregnancy test; all subsequent tests are urine tests.

w Chemistry parameters will include a full chemistry profile (albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen, calcium, chloride, cholesterol, creatinine, glucose, lactate dehydrogenase, magnesium, phosphorus, potassium, sodium, total creatine kinase, total and direct bilirubin, total protein, uric acid). Hematology parameters will include a complete blood count (hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin volume, mean corpuscular volume, mean platelet volume, platelet count, red blood cell distribution width, RBC count, and WBC count) and differential (percent and absolute for the following: basophils, eosinophils, lymphocytes, monocytes, and neutrophils).

6.5 Treatment

6.5.1 Treatment Administered

CORT125134 is a synthetically prepared small molecule with the following chemical name: (R)-(1-(4-fluorophenyl)-6-((1-methyl-1H-pyrazol-4-yl)sulfonyl)-1,4,5,6,7,8-hexahydro-4aH-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone. [redacted]

CORT125134 50-mg capsules are white, size 2, hard gelatin capsules. CORT125134 50-mg capsules will be provided in blister packs containing seven capsules per strip.

6.5.2 Method of Assigning Patients to Groups

Patients who meet all of the inclusion criteria and none of the exclusion criteria (Sections 4.1 and 4.2, respectively, in the study protocol) during the screening period and at baseline (Day 1) will be enrolled in the study. Patients will be enrolled sequentially into two groups. Fifteen patients enrolled in Group 1 will receive 100 mg/day for 4 weeks, then 150 mg/day for 4 weeks, then 200 mg/day for 4 weeks.

Doses for patients enrolled in Group 2 will be 250 mg/day for 4 weeks, then 300 mg/day for 4 weeks, then 350 mg/day for 4 weeks, and then 400 mg for 4 weeks.

Dose escalation decisions will take into account DRC review of PK and safety data.

Patients enrolled in Group 2 who cannot tolerate the starting dose selected for Group 2 will be allowed to continue on study at a lower dose level (eg, 200 or 150 mg). If the lower dose is well tolerated, the dose may be increased by 50 mg after at least 2 weeks of treatment at the lower dose and then escalated every 4 weeks according to the protocol schedule.

All changes in dose, including escalations, escalation window, reductions, and interruptions, must be approved by the Medical Monitor.

6.6 Study Assessments

6.6.1 Demographic and Baseline Characteristics

Patient demographic data will be collected at screening. These include age, sex, race, and ethnicity. Baseline disease characteristics, such as years since diagnosis, and Cushing syndrome type, will also be documented.

6.6.2 Medical History and Medication History

Patient medical history will be obtained at screening, including the diagnosis, etiology, and treatment history of Cushing syndrome (including dexamethasone suppression test

failure where appropriate). Surgery and radiation history will include date and type. A menstrual history will be obtained for all female patients.

6.6.3 Key Efficacy Assessments

The key efficacy assessments in this study are glucose tolerance in the impaired glucose tolerance/diabetes subgroup and BP in the hypertensive subgroup. All other efficacy variables are considered exploratory.

6.6.3.1 Glucose Tolerance

A 2-hour oral glucose tolerance test (oGTT) will be administered to all patients at screening and to patients in the impaired glucose tolerance/diabetes subgroup at baseline (Day 1) and at Weeks 4, 8, and 12/ET for Group 1 and at Weeks 4, 8, 12, and 16/ET for Group 2.

During the 2-hour oGTT, blood samples for plasma glucose and insulin will be collected before the glucose drink and 0.5, 1, 1.5, and 2 hours after the glucose drink.

The oGTT should be performed after an 8-hour fast.

6.6.3.2 Blood Pressure

The 24-hour ambulatory BP will be assessed for all patients during the screening period. For patients who qualify for the hypertension subgroup, there must be a 24-hour ambulatory BP test done within 3 weeks before Day 1. The 24-hour ambulatory BP will also be measured in the hypertension subgroup at Weeks 2, 4, 6, 8, 10, and 12/ET for Group 1 and at Weeks 2, 4, 6, 8, 10, 12, 14, and 16/ET for Group 2.

Mean 24-hour systolic and diastolic ambulatory BP will be obtained by the patient at home using an ambulatory BP monitor provided and initiated at the study site.

6.6.4 Exploratory Efficacy Assessments

6.6.4.1 Physician's Global Assessment

At baseline, Weeks 2, 4, 6, 8, 10, 12/ET, and follow-up visit for Group 1 and at baseline, Weeks 2, 4, 6, 8, 10, 12, 14, 16/ET, and the follow-up visit for Group 2, the Investigator will consider all the patient's signs and symptoms of Cushing syndrome and will rate the degree of illness on a scale of 1 to 9, where 1 = absent and 9 = incapacitating.

6.6.4.2 Glycated Hemoglobin (HbA1c) Concentration

HbA1c is a glycoprotein whose concentration reflects the amount of glucose bound to hemoglobin. It will be assayed in blood samples drawn at baseline (Day 1) and Week 12/ET for Group 1 and at baseline and Weeks 12 and 16/ET for Group 2.

6.6.4.3 Fructosamine Concentration

Fructosamine is a marker used to assess rapid changes in diabetes control and has an excellent correlation with HbA1c. Changes in fructosamine may be observed as early as 2 weeks after beginning dosing with study drug. Serum fructosamine will be assayed in blood samples drawn at baseline (Day 1) and at Weeks 2, 4, 6, 8, 10, and 12/ET for Group 1 and at Weeks 2, 4, 6, 8, 10, 12, 14, and 16/ET for Group 2.

6.6.4.4 Adiponectin Concentration

Adiponectin is a hormone secreted by adipose tissue that modulates glucose regulation and fatty acid metabolism. A blood sample will be collected at baseline (Day 1) and at Weeks 4, 8, and 12/ET for Group 1 and at Weeks 4, 8, 12, and 16/ET for Group 2.

6.6.4.5 24-Hour Urinary Free Cortisol (UFC) with Creatinine

The 24-hour UFC with creatinine test will be measured by tandem mass spectrometry at least two times during each of the following: screening period, and within seven days prior to Weeks 2, 4, 6, 8, 10, and 12/ET for Group 1 and within seven days prior to Weeks 2, 4, 6, 8, 10, 12, 14, and 16/ET for Group 2.

6.6.4.6 Late-Night Salivary Cortisol Test

This test will be performed at least two times during each of the following: screening period, and within seven days prior to the Week 2, 4, 6, 8, 10, and 12/ET visits for Group 1 and within seven days prior to the Week 2, 4, 6, 8, 10, 12, 14, and 16/ET visits for Group 2.

6.6.4.7 Effects on Body Weight and Composition

Body weight will be obtained at screening, baseline (Day 1), and the Week 2, 4, 6, 8, 10, 12/ET, and follow-up visit for Group 1, and the Week 2, 4, 6, 8, 10, 12, 14, 16/ET, and the follow-up visit for Group 2.

Waist circumference will be measured at baseline (Day 1), at Weeks 4, 8, 12/ET, and the follow-up visit for Group 1, and at Weeks 4, 8, 12, 16/ET, and the follow-up visit for Group 2.

6.6.4.8 Beck Depression Inventory

The Beck Depression Inventory (BDI-II) is a 21-question self-report inventory that measures depression. Each answer is scored with values 0 to 3. The total score is determined as the sum of the 21 questions, ranging from 0 to 63. Total scores are classified as mild (<19), moderate (19-29), and severe depression (30-63), with larger scores indicating more severe depressive symptoms. Patients will complete the BDI-II at baseline (Day 1), and Weeks 4, 8, and 12/ET for Group 1 and Weeks 4, 8, 12, and 16/ET for Group 2.

6.6.4.9 Trail Making Test

The Trail Making Test is a neuropsychological test of visual attention and task switching. It consists of two parts in which the patient is instructed to connect a set of 25 dots as quickly as possible while still maintaining accuracy. It can provide information about visual search speed, scanning, processing speed, and mental flexibility, as well as executive functioning. The Trail Making Test is a two part timed test measured in seconds and will be administered at baseline (Day 1) and at Weeks 4, 8, and 12/ET for Group 1 and Weeks 4, 8, 12, and 16/ET for Group 2.

6.6.4.10 CushingQOL

The CushingQoL patient questionnaire evaluates the health-related quality of life in patients with Cushing syndrome (Webb 2008). It comprises 12 questions, each with five possible answers. The CushingQoL instrument addresses known problem areas associated with Cushing syndrome including trouble sleeping, wound healing/bruising, irritability/mood swings/anger, self-confidence, physical changes, ability to participate in activities, interactions with friends and family, memory issues and future health concerns. Lower values reflect lower quality of life. The CushingQoL questionnaire is scored as a total score (ranging from 12 to 60), and is standardized to a scale from 0 (worst QoL) to 100 (best QoL) with the following formula:

$$Y = \frac{(x - 12)}{(60 - 12)} * 100$$

The questionnaire will be administered at baseline (Day 1), at Weeks 4, 8, 12/ET, and the follow-up visit for Group 1, and at baseline and Weeks 4, 8, 12, 16/ET, and the follow-up visit for Group 2.

6.6.4.11 Effects on Metabolism

Lipid panel analysis, which will include total cholesterol, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, very low-density lipoprotein-cholesterol, and triglycerides, will be conducted. Blood will be collected from all enrolled patients at baseline (Day 1), at Weeks 4, 8, 12/ET, and the follow-up visit for Group 1 and at Weeks 4, 8, 12, 16/ET, and the follow-up visit for Group 2.

6.6.4.12 Effect on Strength

The sit-to-stand test will be performed by all enrolled patients and measures the patient's ability to go from standing to sitting in a chair and then getting up again with/without the use of their arms or other aids. The study staff will use a stopwatch to measure the total time it takes for the patient to stand up and sit down five times; start time is in the seated position and stop time is in the final standing position. The sit-to-stand test is measured in seconds and will be administered at baseline (Day 1), at Weeks 4, 8, 12/ET, and the follow-up visit for Group 1 and at Weeks 4, 8, 12, 16/ET, and the follow-up visit for Group 2.

6.6.4.13 Hormonal and Menstrual Cycle Effects

Blood samples will be obtained from each patient for analysis of estradiol, total and free testosterone, sex hormone binding globulin, follicle stimulating hormone, and luteinizing hormone at baseline (Day 1) and at the Week 12/ET visit for Group 1 and at the baseline and Week 16/ET visit for Group 2.

Menstrual cycle information (eg, age at menarche, current pattern of menses, and duration of vaginal bleed) will be recorded, along with any spotting occurrences, at every visit in premenopausal female patients not on hormonal birth control.

6.6.4.14 Coagulation Effects

Blood samples will be obtained for coagulation tests from all enrolled patients at baseline (Day 1), Weeks 4, 8, and 12/ET visits for Group 1 and at Weeks 4, 8, 12, and 16/ET for Group 2. These include activated partial thromboplastin time, Factor VIII, Factor IX, Factor X, and von Willebrand factor, d-dimer, fibrinogen, and thrombin-antithrombin.

6.6.4.15 Glucocorticoid Reception (GR) Activity Biomarkers

A blood sample will be obtained from all patients for analysis of messenger ribonucleic acid (mRNA) expression of glucocorticoid-modulated genes including FKBP5 and a panel of housekeeping genes. For Group 1, samples will be collected at baseline (Day 1), and Weeks 4, 8, and 12/ET; for Group 2, samples will be collected at baseline (Day 1), and Weeks 4, 8, 12, and 16/ET.

Biomarker analysis is outside the scope of this SAP. Biomarker endpoints and analysis methods will be described in a separate Biomarker SAP and Biomarker report.

6.6.4.16 Bone Effects

Blood and urine samples will be obtained from all patients at baseline (Day 1) and Weeks 4, 8, and 12/ET for Group 1 and at baseline and Weeks 4, 8, 12, and 16/ET for Group 2 for analysis of bone markers. These will include urinary N-telopeptides of type 1 collagen (NTx), serum bone alkaline phosphatase, and serum osteocalcin.

6.6.4.17 Hypothalamic-Pituitary-Adrenal (HPA) Axis Effects

Blood samples will be obtained at screening, baseline (Day 1), Weeks 2, 4, 6, 8, 10, and 12/ET for Group 1, and at baseline and Weeks 2, 4, 6, 8, 10, 12, 14, and 16/ET for Group 2 for analysis of plasma adrenocorticotropic hormone (ACTH), serum cortisol, 17-OH-progesterone, 11-deoxycortisol, dehydroepiandrosterone sulfate (DHEA-S), and androstenedione.

6.6.4.18 ACTH Precursors

ACTH precursors (proopiomelanocortin and pro-ACTH) will be measured at baseline (Day 1), Weeks 2, 4, 6, 8, 10, and 12/ET for Group 1 and at baseline and Weeks 2, 4, 6, 8, 10, 12, 14, and 16/ET for Group 2.

6.6.4.19 High-Sensitivity C-reactive Protein

High-sensitivity C-reactive protein is an endothelial inflammation marker. A blood sample will be collected for this assay at baseline (Day 1), Weeks 4, 8, and 12/ET for Group 1 and at baseline and Weeks 4, 8, 12, and 16/ET for Group 2.

6.6.4.20 24-Hour Urine Calcium and Sodium

Increased urinary calcium excretion is a major risk factor in the development of kidney stones in patients with Cushing syndrome. Increased sodium excretion in the urine reflects sodium consumption and is used during the investigation of hypertension as well as in the differential diagnosis of failure of antihypertensive medications or medications that target specific causes of hypertension.

Using the urine samples collected for UFC, calcium and sodium levels will be measured in all patients at screening, baseline (Day 1), Weeks 2, 4, 6, 8, 10, and 12/ET for Group 1 and at baseline and Weeks 2, 4, 6, 8, 10, 12, 14, and 16/ET for Group 2.

6.6.4.21 Insulin-like Growth Factor (IGF)-1

Insulin-like growth factor-1 is a hormone with a structure similar to that of insulin. A blood sample will be obtained from all patients for this determination at baseline (Day 1), Weeks 4, 8, and 12/ET for Group 1 and at baseline and Weeks 4, 8, 12, and 16/ET for Group 2.

6.6.4.22 Thyroid Function Tests

A blood sample will be obtained from all patients for thyroid function tests (free thyroxine [T4], free triiodothyronine [T3], reverse T3, thyroid stimulating hormone) at screening, baseline (Day 1), Weeks 2, 4, 6, 8, 10, and 12/ET for Group 1 and at baseline and Weeks 2, 4, 6, 8, 10, 12, 14, and 16/ET for Group 2.

6.6.5 Description of Safety Variables

Safety will be assessed by physical examination findings, vital signs, ECG results, pregnancy tests, clinical laboratory test results (hematology and chemistry panels), adverse events, and concomitant medications.

6.6.5.1 Physical Examination

A complete physical examination will be conducted at screening, baseline (Day 1), Weeks 2, 4, 6, 8, 10, 12/ET, and the follow-up visit for Group 1 and at baseline and

Weeks 2, 4, 6, 8, 10, 12, 14, 16/ET, and the follow-up visit for Group 2. A complete physical examination will include evaluation of general appearance, HEENT (head, eyes, ears, nose, throat), as well as dermatologic, cardiovascular, respiratory, gastrointestinal, extremities/musculoskeletal, and neurologic body systems.

6.6.5.2 Vital Signs

Vital signs include BP, heart rate, respiratory rate, and oral body temperature, and will be collected in the clinic at screening, baseline (Day 1), Weeks 2, 4, 6, 8, 10, 12/ET, and the follow-up visit for Group 1 and at baseline and Weeks 2, 4, 6, 8, 10, 12, 14, 16/ET, and the follow-up visit for Group 2. Unscheduled assessments of vital signs can be performed as necessary.

Height will be measured at the screening visit only.

6.6.5.3 Electrocardiogram

Twelve-lead ECG tracings will be obtained in triplicate from all patients at screening, Weeks 2, 4, 6, 8, 10, 12/ET, and the follow-up visit for Group 1 and at screening and Weeks 2, 4, 6, 8, 10, 12, 14, 16/ET, and the follow-up visit for Group 2. Patients should be lying down for at least 10 minutes prior to each ECG evaluation. Post-screening ECGs should be performed 2 hours (± 30 minutes) after study drug dosing.

The Investigator or designee will indicate on the site's copy whether the ECG was normal, abnormal but not clinically significant, or abnormal and clinically significant. Any new or worsened abnormality noted as clinically significant will be reported as an AE.

6.6.5.4 Pregnancy Tests

All female patients of childbearing potential (including women <50 years old, women whose surgical sterilization was performed <6 months ago, and women who have had a menstrual period in the last two years) will take pregnancy tests at every visit from screening through follow-up. The screening pregnancy test will be a blood test; all subsequent pregnancy tests will be urine tests.

6.6.5.5 Safety Clinical Laboratory Tests

Fasting blood samples will be collected for labs in all patients at screening, baseline (Day 1), Weeks 2, 4, 6, 8, 10, 12/ET, and the follow-up visit for Group 1, and at baseline and Weeks 2, 4, 6, 8, 10, 12, 14, 16/ET, and the follow-up visit for Group 2. Laboratory samples will be analyzed at one or more central laboratories.

Laboratory values for an analyte that are outside of the normal range for that analyte per the applicable central laboratory will be identified and can be repeated at the Investigator's discretion. The Investigator will determine if any out-of-range laboratory values that emerge during the study are clinically significant.

Safety laboratory measurements will include the following:

- Chemistry:
    - Full chemistry profile: albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen, calcium, chloride, total cholesterol, creatinine, glucose, lactate dehydrogenase, magnesium, phosphorus, potassium, sodium, total creatinine kinase, total and direct bilirubin, total protein, and uric acid
- Hematology:
    - Complete blood count: hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, mean platelet volume, platelet count, red blood cell distribution width, red blood cell (RBC) count, and white blood cell (WBC) count
    - Differential: percent and absolute for the following: basophils, eosinophils, lymphocytes, monocytes, and neutrophils

6.6.5.6 Adverse Events

An AE is any untoward medical occurrence in a study patient administered a pharmaceutical product, which does not necessarily have to have a causal relationship with this treatment. Collection of AEs will start immediately following signing of the informed consent form and will continue throughout the study.

AEs that occur after the start of study treatment up to and including 28 days after administration of the last dose of study drug will be considered treatment-emergent adverse events (TEAEs). AEs will be evaluated for incidence, severity, relationship to the study medication, seriousness of the AE, and what action was taken.

6.6.5.7 Prior and Concomitant Medications

Concomitant medications are defined as any prescription or over-the-counter medication, herbal preparations, and vitamin and/or mineral supplements that the patient began or continued in the period starting with the first dose of study medication on Day 1 and ending at the follow-up visit. Medications that the patient started and ended before the first dose of study drug will be noted as prior medications.

Prior and concomitant medications are collected at every visit from screening through follow-up.

6.6.6 Description of Pharmacokinetics

Pharmacokinetic analysis is outside the scope of this SAP; PK endpoints and analysis methods will be described in a separate PK Analysis Plan and PK Study Report.

6.7 Data Quality Assurance

During the conduct of the study and until completion of the CSR, monitor(s) representing Corcept Therapeutics will visit the investigator(s) at regular intervals, to assure that the study is conducted under ICH E6 (Good Clinical Practice), including monitoring for study progress, completeness, consistency and accuracy of data entered on the electronic case report forms (eCRFs), review of outstanding data discrepancies and other aspects of study conduct. The investigator (or designee) is required to cooperate with the monitor. Laboratory tests will be analyzed at a selected central laboratory. If required, these data will be supplemented by laboratory tests from a site's local laboratory. Data management will be performed by an outside CRO. Electronic case report form data will be subject to EDC database batch validations run per programmed edit specifications. Data Management will conduct data listing reviews. Data queries will be reviewed and closed upon resolution. Case report form processing will continue until all eCRFs are received and are "clean" (defined as passing all edit specifications, and review of the medical monitor and biostatistics group). All reported serious adverse events (SAEs) will be coded to standard system organ class and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA version 19.0) terminology. Medications will be coded using the World Health Organization (WHO Drug version 161E, enhanced) dictionary. Medications entered on the eCRF will be mapped to Anatomic Therapeutic Chemical (ATC) drug class (level 4) and drug name.

Report summaries will be generated using validated Base SAS® software, version 9.4 or higher, on a PC or server-based platform. Additional validated software may be used to generate analyses, as needed.

All SAS programs that create outputs or supporting analysis datasets will be validated per vendor standard operating procedures.

The content of the source data will be reviewed on an ongoing basis by project statistical programmers and statisticians as appropriate, per vendor standard operating procedures.

7 STATISTICAL METHODS

7.1 General Methodology

Data will be analyzed by Precision for Medicine, Oncology and Rare Disease biostatistics personnel. Statistical analyses will be reported with tables, figures, and listings, presented in rich text format, and using recommended ICH numbering. Output specifications for all tables, figures, and listings will be in conformance with guidelines specified by the ICH in Appendix 7 of the *Electronic Common Technical Document Specification* (Apr 2003).

In addition to tables, figures, and listings, individual patient profiles will be generated to display select efficacy and safety endpoints over time, to include data from each patients' entire time on study drug.

7.1.1 Reporting Conventions

Listings will be ordered by Group 1 and Group 2, site, patient number, and assessment or event date. Listings presenting study data over time will include the dose level the patient received at the time of data collection.

Continuous variables will be summarized to indicate the population sample size (N), number of patients with available data (n), mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by the population size (N), number of patients with available data (n), number of patients in each category, and the percentage of patients in each category. Unless otherwise noted, the denominator to determine the percentage of patients in each category will be based on the number of patients with available data (n). Select ordinal data may be summarized using both descriptive statistics and counts and percentages of patients in each category, as appropriate.

Non-zero percentages will be rounded to two decimal places. Rounding conventions for presentation of summary statistics will be based on the precision of the variable of summarization, as it is collected in its rawest form (ie, on the eCRF or as provided within an external file) and are outlined as follows:

- The mean and median will be rounded to one more decimal place than the precision of the variable of summarization;
- Measures of variability (eg, SD, SE) will be rounded to two more decimal places than the precision of the variable of summarization; and
- Minimum and maximum values will be presented using the same precision as the variable of summarization.

Other statistics (eg, CIs) will be presented using the same general rules outlined above, or assessed for the most appropriate presentation based on the underlying data.

All statistical tests will be conducted at the two-sided, 0.05 level of significance, unless otherwise specified.

7.1.2 Definition of Analysis Visit Windows

In analysis of data summarized by study visit, unscheduled and early termination visits will be reassigned a study visit where data is scheduled for collection based on the actual days relative to baseline.

Table 2 defines the visit windows for the assessments taken at biweekly intervals to be established for Group 1 with respect to relative day from the start of study drug.

Table 2 Group 1 Biweekly Interval Visit Windows (Days)

Visit	Target Study Day	Analysis Window Study Day	
		Low	High

Baseline	1	Reference Section 7.1.5 for endpoint-specific definition	
Week 2	14	> Baseline measurement	21
Week 4	28	22	35
Week 6	42	36	49
Week 8	56	50	63
Week 10	70	64	77
Week 12	84	78	98

Table 3 defines the visit windows for the assessments taken at biweekly intervals to be established for Group 2 with respect to relative day from the start of study drug.

Table 3 Group 2 Biweekly Interval Visit Windows (Days)

Visit	Target Study Day	Analysis Window Study Day	
		Low	High
Baseline	1	Reference Section 7.1.5 for endpoint-specific definition	
Week 2	14	> Baseline measurement	21
Week 4	28	22	35
Week 6	42	36	49
Week 8	56	50	63
Week 10	70	64	77
Week 12	84	78	91
Week 14	98	92	105
Week 16	112	106	126

Table 4 defines the visit windows for the assessments taken at monthly intervals to be established for Group 1 with respect to the relative day from the start of study drug.

Table 4 Group 1 Monthly Interval Visit Windows (Days)

Visit	Target Study Day	Analysis Window Study Day	
		Low	High
Baseline	1	Reference Section 7.1.5 for endpoint-specific definition	
Week 4	28	> Baseline measurement	42
Week 8	56	43	70
Week 12	84	71	98

Table 5 defines the visit windows for the assessments taken at monthly intervals to be established for Group 2 with respect to the relative day from the start of study drug.

Table 5 Group 2 Monthly Interval Visit Windows (Days)

Visit	Target Study Day	Analysis Window Study Day	
		Low	High
Baseline	1	Reference Section 7.1.5 for endpoint-specific definition	
Week 4	28	> Baseline measurement	42
Week 8	56	43	70
Week 12	84	71	98

Week 16	112	99	126

The Week 16 follow-up window for Group 1 patients will include all unscheduled or scheduled follow-up visits occurring after the Week 12 visit window if patient is no longer on study drug. The Week 20 follow-up window for Group 2 patients will include all unscheduled or scheduled follow-up visits occurring after the Week 16 visit window if patient is no longer on study drug. If an unscheduled or scheduled visit occurs after the upper bound of the Week 12 (Group 1) or Week 16 (Group 2) visit window, and patient is still on study drug, that visit will be included in the Week 12 (Group 1) or Week 16 (Group 2) visit window, as appropriate.

Data collected at scheduled visits will be analyzed based on the nominal visit as reported in the database (ie, will not be mapped to visit windows). If an unscheduled visit is mapped to a visit window that already has a non-missing assessment for the corresponding scheduled visit, the scheduled visit will be used in the analysis. Otherwise, if multiple visits occur within a single visit window, then the closest visit to the target day of the visit window will be used in the analysis. If there is a tie, the later visit will be used in the analysis.

In situations where a time point is missing in the oGTT measurements, preference for visit windowing will be given to another visit (scheduled or unscheduled) occurring in the same visit window that has complete oGTT data. If more than one alternative visit is available, preference should be given to the closest visit to the target day of the visit window.

If early termination data is not labeled separately from the Week 12 visit in Group 1 or the Week 16 visit in Group 2 in the clinical database or external data transfers, then that visit data will be considered early termination data if the disposition eCRF indicates the patient discontinued the study early, and will be reassigned to the appropriate analysis visit window according to Tables 2-5, above. Otherwise, that visit data will be considered Week 12 or Week 16 data, as appropriate.

7.1.3 Data Handling Rules

Unless otherwise noted, values reported as greater than or less than some quantifiable limit (eg, "<1.0") will be summarized with the sign suppressed in summary tables and figures, using the next rounded down tenths place ½ step (eg, .5 or .0). Examples are provided in Table 6. Data will display on patient listings to include the sign.

Table 6 Examples of Data Handling Rules

Laboratory Test	Raw Data Value	Assigned Values for Analysis
11-deoxycortisol	<0.58	0.5
Plasma ACTH	<1.1	1
Salivary Cortisol	<0.8	0.5

7.1.4 Standard Calculations

Where appropriate, the calculated study day of each assessment or event will be presented with the assessment or event date on patient data listings, where study day will be determined as:

- The assessment/event date minus the date of first dose, if the assessment/event date is prior to the date of first dose; and
- The assessment/event date minus the date of first dose, plus one, if the assessment/event date is on or after the date of first dose.

Other variables requiring calculations will be derived using the following formulas:

- **Days:** A duration between two dates expressed in days will be calculated using the following conventions:
    - (Later date – earlier date) + 1, if the earlier date is on or after the date of first dose of study drug; or
    - Later date – earlier date, if the earlier date is prior to the date of first dose of study drug.
- **Months:** A duration expressed in months will be calculated by dividing the duration in days by (365.25 / 12);
- **Years:** A duration expressed in years will be calculated by dividing the duration in days by 365.25;
- **Change from Baseline:** Change from baseline will be calculated as the post-baseline value minus the baseline value;
- **Percentage Change from Baseline:** Percentage change from baseline will be calculated as the change from baseline divided by the baseline value, multiplied by 100.

7.1.5 Definitions of Baseline

The baseline for oGTT plasma glucose and insulin is defined as the last oGTT corresponding time point measurement prior to first dose of study drug (eg, pre-glucose drink, 0.5 hours post-glucose drink, 1 hour post-glucose drink, etc.). For example, the baseline for all post-baseline 0.5 hour post-glucose drink time points will be the last 0.5 hour post-glucose drink time point prior to first dose of study drug. In situations where a time point is missing in the oGTT measurements, preference for baseline will be given to another visit occurring prior to first dose of study drug, if available, where all time points are non-missing (eg, if a Day 1 oGTT time point is missing, and a Screening visit with no missing time points is available, that Screening visit will be flagged as baseline). If more

than one alternative visit is available (scheduled or unscheduled), preference should be given to the last visit prior to first dose of study drug.

The baseline for the area under the concentration-time curve for glucose ($AUC_{glucose}$) and insulin ($AUC_{insulin}$) is defined at the same visit (unscheduled or scheduled) that the oGTT plasma glucose and insulin baseline is defined.

The baseline for 24-hour UFC with creatinine, late-night salivary cortisol, 24-hour urine calcium, and 24-hour urine sodium is defined as the average of all measurements prior to first dose of study drug, including unscheduled visits.

The baseline for twelve-lead ECG interval parameters is defined as the average of the triplicate readings at the last visit prior to first dose of study drug. The last visit prior to first dose of study drug may by an unscheduled or scheduled visit.

The baseline for all other efficacy and safety parameters not previously mentioned is defined as the last measurement prior to first dose of study drug. The last visit prior to first dose of study drug may be an unscheduled or scheduled visit.

7.2 Analysis Populations

The analysis populations are defined as follows:

- Safety Population: Includes all enrolled patients who receive at least one dose of study drug.

- Modified Intent-to-Treat (mITT) Population: Includes all enrolled patients who receive at least one dose of study drug and have non-missing post-baseline data collected.

All efficacy analyses will be performed on the mITT Population. All safety analyses will be performed on the Safety Population; select safety analyses may also be performed on the mITT Population.

As a sensitivity analysis of the key efficacy endpoints, a modified version of a Per-Protocol Population will also be used, defined as follows:

- Modified Per-Protocol (mPP) Sensitivity Population: Includes all patients in the mITT Population with exclusions at specific visits per patient based on clinical judgment and/or major or important protocol deviations that are applied on a visit and outcome level rather than patient level. For example, a patient with a major or important protocol deviation occurring between Week 10 and Week 12 may have data included in analyses prior to Week 12 but be dropped from the Week 12 analysis.

The mPP Sensitivity Population may also be used as a sensitivity analysis for select exploratory efficacy and safety endpoints.

7.3 Examination of Subgroups

The following subgroups are defined for the study analyses:

1. Dose groups:
    a. Group 1: Patients enrolled plan to receive 100 mg of study drug for 4 weeks, followed by 150 mg for 4 weeks, and then 200 mg for 4 weeks.
    b. Group 2: Patients enrolled plan to receive 250 mg of study drug for 4 weeks, followed by 300 mg for 4 weeks, then 350 mg for 4 weeks, and then 400 mg for 4 weeks.
2. Cushing syndrome comorbidity:
    a. Patients with type 2 diabetes or impaired glucose tolerance (IGT): Confirmed at screening visit with either a fasting glucose > 126 mg/dL and a 2-hour oGTT result for plasma glucose ≥ 200 mg/dL at 2 hours (for type 2 diabetes), or a 2-hour oGTT result for plasma glucose in the range of ≥ 140 mg/dL to < 200 mg/dL (for impaired glucose tolerance).
    b. Patients with hypertension (HT): Confimed at screening with a mean systolic BP of 130-170 mmHg and/or a mean diastolic BP of 85-110 mmHg based on the 24-hour ambulatory BP measurement.
3. Etiology:
    a. ACTH-Dependent: Cushing disease or ectopic
    b. Adrenal
4. Mildly depressive patients: Patients whose baseline BDI-II total score is less than 19.
5. Concomitant medications in the IGT Cushing syndrome comorbidity subgroup:
    a. Patients who did not receive exogenous insulin at baseline
    b. Patients who did not receive exogenous insulin during the treatment period
6. Menopausal status:
    a. Pre-menopausal
    b. Post-menopausal
7. Low serum osteocalcin patients: Patients whose baseline serum osteocalcin measurement is less than 8 μg/L.

8. High HbA1c patients: Patients whose baseline HbA1c measurement is ≥ 6.5%.

As a general rule, all efficacy data summaries will be presented by Group 1 and Group 2; all safety data summaries will be presented by Group 1, Group 2, and Overall. Data summaries by other subgroups will be implemented as described in this SAP.

7.4 Time-Course and Dose-Course Analysis Methods

Because of potential events that can affect the planned dose escalations of the study (eg, individual dose escalation timing that differs from planned nominal time, dose reduction, dose interruption, and/or dose discontinuation), the data will be summarized using the following two methods:

- Time-course (by visit), which evaluates assessments across visits and assumes protocol-defined dose-escalation; and

- Dose-course (by dose categories), which evaluates assessments according to expected dose level received, as defined by the Medical Monitor.

Time-course will be used as the primary method of analysis for efficacy assessments, and will follow the analysis visit windowing described in Section 7.1.2.

Dose-course will be used as the primary method of analysis for safety assessments, and as a sensitivity method of analysis for efficacy assessments, including all key and exploratory efficacy assessments. Dose-course categories include 100, 150, 200, 250, 300, 350, and 400 mg, and when assessments are summarized by Group 1 and Group 2, the following categories will be used for each:

- Group 1: 100, 150, and 200 mg dose levels; and

- Group 2: ≤ 200, 250, 300, 350, and 400 mg dose levels.

The ≤ 200 mg dose level is included to account for Group 2 patients who may have their study drug dose reduced to 200 mg or less. The date of study drug dose administration per patient will be used to determine which dose-course level assessments fall in, and the last assessment available per patient within each dose-course level will be used as the final assessment for that dose level in the analysis. For example, if a patient dosed at 250 mg, reduced to 200 mg, and escalated again to 250 mg, all assessments will be gathered where the patient was dosing at 250 mg, and the last available assessment will be used in the analysis at the 250 mg dose level.

Dose-course categories will also include the follow-up period, where appropriate, and will be defined as the last assessment available for all assessments occurring after the date of last dose of study drug per patient.

7.5 Study Patients

7.5.1 Disposition of Patients

Patient disposition will be summarized for the Safety and mITT populations by Group 1, Group 2, and over all patients combined. Summaries will include the number and percentage of patients within each comorbidity subgroup (IGT/HT), etiology subgroup, completing the study, and terminating the study early by the primary reason for discontinuation.

A summary including all patients will also be presented, including the number and percentage of patients screened, screen failures, and patients in each analysis population by Group 1, Group 2, and all patients combined.

7.5.2 Protocol Deviations

Major and important protocol deviations, as collected by the Corcept team, will be summarized by Group 1, Group 2, over all patients combined, for the Safety Population. Refer to the Protocol Deviations Plan, developed under ICH E3 and ICH E3 Q&A (2012) for the definitions of protocol deviations and deviations categories.

The number and percentage of patients with any major or important protocol deviations as well as the number and percentage of patients with deviations within each category will be presented.

All major and important protocol deviations will be determined and appropriately categorized prior to database lock by the Corcept study team. Protocol deviations will be listed by Group 1, Group 2, study site, patient, and date of deviation, and will indicate if they are considered major or important.

7.6 Efficacy

As described in Section 7.4, efficacy endpoints will be primarily summarized using a time-course method of analysis (by visit), and secondarily summarized using a dose-course method of analysis (by dose categories). Although the longitudinal summaries in the below efficacy sections are described using the time-course method of analysis, language that specifies “visit” is meant to be replaceable with “dose category” when analyses are repeated using the dose-course method of analysis.

All efficacy data will appear in by-patient data listings.

7.6.1 Demographic and Baseline Characteristics

Demographic variables including age at the time of informed consent, sex, ethnicity and race, will be summarized for the Safety and mITT populations, comorbidity subgroup, and etiology subgroup by Group 1, Group 2, and overall patients combined.

Age will be summarized using descriptive statistics. Sex, ethnicity, and race will be summarized with the number and percentage of patients in each parameter category.

Baseline characteristics include medical history, baseline disease characteristics (eg, time since diagnosis, Cushing syndrome type), height, weight, body mass index (BMI), waist circumference, plasma ACTH, 24-hr UFC with creatinine, late-night salivary cortisol, fructosamine, oGTT plasma glucose, $AUC_{glucose}$, $AUC_{insulin}$, HbA1c, osteocalcin, and mean 24-hour systolic and diastolic BP from ambulatory BP monitoring. BMI will be calculated as: weight (kg) / [height (cm) / 100]^2. $AUC_{glucose}$ and $AUC_{insulin}$ definitions can be found in Sections 7.6.3.2.1 and 7.6.3.2.3, respectively.

The baseline characteristics and baseline disease characteristics summary tables will be summarized for all patients in the Safety and mITT populations and presented by etiology subgroups, by Group 1, Group 2, and over all patients combined. Medical history will be summarized for all patients in the Safety Population and presented by etiology subgroup, by Group 1, Group 2, and over all patients combined. Continuous variables at baseline will be summarized using descriptive statistics. Frequency counts and percentages to summarize patients reporting medical history by system organ class (coded using MedDRA version 19.0) and Cushing syndrome history will be presented. Time (months) since diagnosis of Cushing disease will be calculated as the informed consent date minus the diagnosis date from the medical history eCRF, and be will be summarized using descriptive statistics. If the diagnosis date of Cushing disease is incomplete, month will be imputed as the first month of the year, and day will be imputed as the first day of the month. Missing year will not be imputed.

7.6.2 Measurements of Treatment Compliance

Compliance to the study treatment regimen will be determined as the total actual dose received divided by the expected dose received, multiplied by 100. A patient is considered compliant to the treatment regimen if their compliance calculation is ≥ 80% of the expected dose. Expected dose received will be calculated as [(study drug stop date – study drug start date) + 1] x dose expected on those days, and will reflect physician decision per patient. Total actual dose received will be calculated as the number of capsules taken per visit x 50 mg, summed across all visits per patient. Dosing compliance will be summarized using descriptive statistics, by Group 1 and Group 2, based on the Safety Population. The number and percentages of patients who are < 80% compliant and ≥ 80% compliant within each group will be summarized.

7.6.3 Key Efficacy Endpoint Analysis Methods

Key efficacy endpoints will be performed on the mITT Population. As a sensitivity analysis, key efficacy endpoints will also be performed using the mPP Sensitivity Population.

7.6.3.1 Medications Affecting Responder Analyses

Patients who start an additional medication of interest during the treatment period or increase the dosage of a concurrent medication of interest will be classified as

nonresponders in the responder analyses for $AUC_{glucose}$ (Section 7.6.3.2.1) and mean systolic and diastolic BP (Section 7.6.3.3.1). Concomitant medications of interest for the $AUC_{glucose}$ responder analysis include diabetes medications, as indicated by the Medical Monitor. Likewise, concomitant medications of interest for the mean systolic and diastolic BP responder analysis include antihypertensive medications, as indicated by the Medical Monitor.

7.6.3.2 Impaired Glucose Tolerance/Diabetes Subgroup Analyses

Summary tables and figures will be repeated by the concomitant medications subgroup including patients who did not receive exogenous insulin during the treatment period. Insulin, HOMA-IR, and Matsuda Index endpoints will also be repeated by the concomitant medication subgroup including patients who did not receive exogenous insulin at baseline.

7.6.3.2.1 oGTT Plasma Glucose Responder Analysis

$AUC_{glucose}$ will be calculated based on results of the 2-hour oGTTs taken at baseline, Week 4, Week 8, Week 12, and Week 16 (Group 2 only), for those patients with impaired glucose tolerance or diabetes at study entry. The AUCs will be calculated using the linear trapezoidal rule, as follows (where C_1 and C_2 are concentrations at times t_1 and t_2, respectively):

$$AUC = \frac{1}{2}(C_1 + C_2)(t_2 - t_1)$$

A responder will be defined as a patient who experiences at least a 25% decrease from baseline in $AUC_{glucose}$ who has not taken an additional diabetes medication during the treatment period or increased the dosage of a concurrent diabetes medication, as indicated by the Medical Monitor. Nonresponder rules apply as described in Section 7.6.3.1. The responder endpoint will be calculated at each visit. The primary efficacy endpoint is the Week 12/ET time point for Group 1, and the Week 16/ET time point for Group 2, which will be summarized as Last Observed (Section 7.6.5.1). The number and percentage of patients who are responders will be presented by Group 1 and Group 2, along with a 95% exact binomial two-sided CI (Clopper-Pearson).

There will additionally be a threshold test on the lower limit of the 95% exact binomial CI. The null hypothesis to be tested is that there is no difference between the rate of spontaneous remission of Cushing syndrome and the responder rate due to study drug:

$$H_0: \pi_{responder} \leq 0.2;$$

Where π represents the lower limit of the 95% exact binomial CI of responders. The alternative hypothesis to be tested is that there is a difference between the rate of spontaneous remission of Cushing syndrome and the responder rate due to study drug:

$$H_1: \pi_{responder} > 0.2;$$

Where the null hypothesis will be rejected in favor of the alternative if the lower limit of the 95% exact binomial CI for the responder rate is greater than 20%. Although there are anecdotal reports of spontaneous remission in Cushing syndrome, the cases are extremely rare. Twenty percent (20%) is an appropriate threshold to test against in this population, given that the spontaneous remission rate in individuals who are eligible for this study is close to 0%. These rare cases often occur in the setting of de novo Cushing disease and have been largely due to apoplexy (pituitary hemorrhage). Patients who are enrolled with prior pituitary radiotherapy could theoretically lead to a higher remission rate. Although the criteria used for establishing remission are not standardized, recent reviews document that the usual time to remission in those patients who respond is approximately 2 years depending on the modality of radiotherapy used. While control of hypercortisolism may occur in as many as 50-60% of patients in 3-5 years, responses are gradual, variable, and may be delayed for many years (Fleseriu, et al 2012).

$AUC_{glucose}$ will be summarized using descriptive statistics including two-sided 95% CI of the mean, the geometric mean, and arithmetic CV (%), by Group 1 and Group 2. In addition, the following analyses of the continuous $AUC_{glucose}$ endpoint will be conducted:

- A Wilcoxon signed-rank test will be conducted to evaluate if there is a significant change compared to baseline at each visit.

- For each group, a restricted maximum likelihood (REML) based linear mixed model for repeated measures (MMRM) analysis will be calculated for both $AUC_{glucose}$ and the natural log of $AUC_{glucose}$. The model will use visit as a fixed effect and patient as a random effect. A compound symmetry covariance structure will be used to model the within-patient errors; Autoregressive (1) and Toeplitz structures will also be explored. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Least-squares means will be used to estimate the change from baseline treatment effect at each visit.

Additionally, a cumulative distribution for percent change in $AUC_{glucose}$ from baseline to each visit will be presented and sorted by most improved to least improved.

A plot of mean $AUC_{glucose}$ will be presented over time by Group 1 and Group 2. A waterfall plot of $AUC_{glucose}$ percent change from baseline to last observed by dose level and during the treatment period will be presented by Group 1 and Group 2.

7.6.3.2.2 oGTT Plasma Glucose

Plasma glucose (mmol/L) will be summarized using descriptive statistics including two-sided 95% CI of the mean by visit, time point (pre-glucose drink and 0.5, 1, 1.5, and 2 hours post glucose drink), by Group 1, and Group 2, to include the change from baseline. Plasma glucose (mmol/L) will also be analyzed by a Wilcoxon signed-rank test to evaluate if there is a significant change compared to baseline at each time point (pre-glucose drink and 0.5, 1, 1.5, and 2 hours post glucose drink). A column summarizing change from pre-glucose drink values will also be included.

A plot of mean plasma glucose (mmol/L) values over time will be presented by Group 1 and Group 2.

7.6.3.2.3 oGTT $AUC_{insulin}$

Change from baseline in $AUC_{insulin}$ will be calculated and summarized similar to $AUC_{glucose}$, including the Wilcoxon signed-rank test and MMRM modeling. A responder analysis will not be done using $AUC_{insulin}$. A plot of mean $AUC_{insulin}$ will be presented over time by Group 1 and Group 2. $AUC_{insulin}$ analyses will also be presented by concomitant medication subgroups.

7.6.3.2.4 oGTT Insulin

Insulin (µU/mL) will be summarized similar to oGTT plasma glucose (mmol/L). Plots of mean insulin (µU/mL) will be presented over time by Group 1 and Group 2. Insulin (µU/mL) analyses will also be presented by concomitant medication subgroups.

7.6.3.2.5 HOMA-IR

Plasma glucose (mmol/L) and insulin (µU/mL) pre-glucose drink values from the oGTTs will be used to calculate the homeostatic model assessment for insulin resistance (HOMA-IR) as follows:

$$HOMA - IR = \frac{glucose\ \left(\frac{mmol}{L}\right) x\ insulin\ (\mu\frac{\mathrm{U}}{\mathrm{mL}})}{22.5}$$

HOMA-IR will be summarized using descriptive statistics including two-sided 95% CI of the mean by visit, Group 1, and Group 2, to include the change from baseline. HOMA-IR will also be analyzed by a Wilcoxon signed-rank test to evaluate if there is a significant change compared to baseline at each visit.

Box plots of HOMA-IR will be presented over time by Group 1 and Group 2. HOMA-IR analyses will also be presented by concomitant medication subgroups.

7.6.3.2.6 Matsuda Index

Plasma glucose (mmol/L) and insulin (µU/mL) from the oGTTs will be used to calculate the Matsuda index, which is an index created to evaluate the whole body physiological insulin sensitivity from data obtained by oGTTs (Matsuda 1999), as follows:

$$Matsuda\ index = \frac{10000}{\sqrt{g_0 * 18 * i_0 * \frac{(g_0 + g_{0.5} * 2 + g_1 * 2 + g_{1.5} * 2 + g_2)}{8} * 18 * \frac{(i_0 + i_{0.5} * 2 + i_1 * 2 + i_{1.5} * 2 + i_2)}{8}}}$$

Where *g* corresponds to plasma glucose (mmol/L), *i* corresponds to insulin (µU/mL), and the subscripts 0, 0.5, 1, 1.5, and 2 correspond to the time points in hours during the oGTT test (eg, 0 = pre-glucose drink, 0.5 = 0.5 hours after glucose drink, etc.). The Matsuda

index will be summarized using descriptive statistics including two-sided 95% CI of the mean by visit, Group 1, and Group 2, to include the change from baseline. The Matsuda index will also be analyzed by a Wilcoxon signed-rank test to evaluate if there is a significant change compared to baseline at each visit. Matsuda index analyses will also be presented by concomitant medication subgroups.

7.6.3.2.7 Change in Blood Glucose Medications

The number and percentage of patients whose dose of medications that lower blood glucose decreased, stayed the same, or increased from baseline to study drug dose level or follow-up period, as determined by blood glucose medication start date, will be summarized, among those patients taking such medication at baseline. Additional counts and percentages will be provided including patients who were not taking blood glucose medications at baseline.

7.6.3.3 Hypertension Subgroup Analysis Methods

Change in mean diastolic and systolic BP measured by 24-hour ambulatory BP monitoring will be analyzed for patients with hypertension at study entry. The mean BP value per patient per visit will be included in the analysis if the record is labeled as "PASS" in the corresponding overall quality control (QC) variable provided by the external ambulatory BP vendor.

7.6.3.3.1 Blood Pressure Responder Analysis

A responder will be defined as a patient who experiences at least a 5 mmHg decrease in mean diastolic or systolic BP from baseline who has not taken an additional antihypertensive medication during the treatment period or increased the dosage of a concurrent antihypertensive medication, as indicated by the Medical Monitor. Nonresponder rules apply as described in Section 7.6.3.1. The responder endpoint will be calculated at each visit. The primary efficacy endpoint is the Week 12/ET time point for Group 1, and the Week 16/ET time point for Group 2, which will be summarized as Last Observed (Section 7.6.5.1). The number and percentage of patients who are responders will be presented by Group 1 and Group 2, along with a 95% exact binomial two-sided CI (Clopper-Pearson). BP will also be summarized using descriptive statistics, including two-sided 95% CI of the mean, and a Wilcoxon signed-rank test to evaluate if there is a significant change compared to baseline at each time point.

There will additionally be a threshold test on the lower limit of the 95% exact binomial CI. The null hypothesis to be tested is that there is no difference between the rate of spontaneous remission of Cushing syndrome and the responder rate due to study drug:

$$H_0: \pi_{responder} \leq 0.2;$$

Where π represents the lower limit of the 95% exact binomial CI of mean systolic or diastolic BP responders. The alternative hypothesis to be tested is that there is a difference between the rate of spontaneous remission of Cushing syndrome and the responder rate due to study drug:

$$H_1: \pi_{responder} > 0.2;$$

Where the null hypothesis will be rejected in favor of the alternative if the lower limit of the 95% exact binomial CI for the responder rate is greater than 20% (Fleseriu, et al 2012; also reference Section 7.6.3.2.1).

Also, as sensitivity analyses, the BP responder analysis will be repeated using the following criteria:

1. A patient is considered a responder if once the patient meets the responder criteria (established above), the patient continues to meet it throughout any remaining post-baseline visits. This responder endpoint will be calculated only at the end of the study considering all post-baseline visits.

2. A patient is considered a responder if the patient experiences at least a 5 mmHg decrease in mean diastolic or systolic BP from baseline. Additionally, if a patient has a decrease in systolic BP and an increase in diastolic BP, or vice versa, the patient will be classified as a nonresponder. The responder endpoint will be calculated at each visit.

3. A patient is considered a responder by the criteria established in #2 and the patient maintains responder status throughout any remaining post-baseline visits. The responder endpoint will be calculated only at the end of the study considering all post-baseline visits.

4. A patient is considered a responder if the patient experiences a reduction in the number or dose of antihypertensive medications, as indicated by the Medical Monitor, without experiencing a worsening of either systolic or diastolic BP. The responder endpoint will be calculated at each visit.

5. A patient is considered a responder if the criteria established in #2 and/or #4 is met.

Nonresponder rules, as described in Section 7.6.3.1, apply to the sensitivity responder analyses.

Additionally, cumulative distributions for change in systolic and diastolic BP from baseline to each visit will be presented and sorted by most improved to least improved.

7.6.3.3.2 24-Hour Ambulatory Blood Pressure

Mean 24-hour diastolic and systolic BP, mean daytime diastolic and systolic BP, and mean nighttime diastolic and systolic BP will be summarized using descriptive statistics including two-sided 95% CI of the mean by visit, Group 1, and Group 2, to include the change from baseline. Diastolic and systolic BP will also be analyzed by a Wilcoxon signed-rank test to evaluate if there is a significant change compared to baseline at each visit. Daytime diastolic and systolic BP is defined as those BP measurements collected

between 9am to 9pm. Nighttime diastolic and systolic BP is defined as those BP measurements collected between 1am to 6am.

A plot of mean 24-hour systolic and diastolic BP values over time by Group 1 and Group 2 will be presented. Waterfall plots of mean systolic and diastolic change from baseline to last observed by dose level and overall will be presented by Group 1 and Group 2. Plots of mean daytime and nighttime systolic and diastolic BP will also be presented over time by Group 1 and Group 2.

7.6.3.3.3 Change in Antihypertensive Medications

The number and percentage of patients whose dose of antihypertensive medication decreased, stayed the same, or increased from baseline to study drug dose level or follow-up period, as determined by antihypertensive medication start date, will be summarized, among those patients taking such medications at baseline. Additional counts and percentages will be provided including patients who were not taking antihypertensive medications at baseline.

7.6.4 *Exploratory Efficacy Endpoint Analysis Methods*

All exploratory efficacy analyses will be performed on the mITT populations. As a sensitivity analysis, select exploratory efficacy endpoints will also be performed using the mPP Sensitivity Population.

The exploratory efficacy assessments of fructosamine and adiponectin concentrations will be summarized using descriptive statistics including two-sided 95% CI of the mean by visit and Group 1 and Group 2, to include the change from baseline. These efficacy assessments will also be analyzed by a Wilcoxon signed-rank test to evaluate if there is a significant change compared to baseline at each visit.

The exploratory efficacy assessments of 24-hour UFC with creatinine, late-night salivary cortisol, 24-hour urine calcium, and 24-hour urine sodium will be summarized using descriptive statistics including two-sided 95% CI of the mean by visit and Group 1 and Group 2, to include the change from baseline. These efficacy assessments will also be analyzed by a Wilcoxon signed-rank test to evaluate if there is a significant change compared to baseline at each visit. All post-baseline measurements will be averaged per patient per visit. As a sensitivity analysis, repeat tables of these exploratory efficacy assessments will be produced using baseline defined as the average of the two worst measurements prior to first dose of study drug. 24-hour UFC with creatinine will additionally be summarized over the etiology subgroups.

Other exploratory efficacy assessments will be summarized using descriptive statistics including two-sided 95% CI of the mean by parameter, visit, time point (where appropriate), and Group 1 and Group 2, to include the change from baseline. Where appropriate, efficacy assessments will also be analyzed by a Wilcoxon signed-rank test to evaluate if there is a significant change compared to baseline at each visit. See the following list of included exploratory efficacy assessments:

- Physician's global assessment
- HbA1c
- Body weight and waist circumference
- BDI-II
- Trail Making Test
- CushingQOL
- Lipid panel
- Sit-to-stand test
- Hormonal effects
- Coagulation tests
- Bone markers
- HPA axis markers
- ACTH precursors
- High-sensitivity C-reactive protein
- IGF-1
- Thyroid function tests

HbA1c results will also be summarized by the high HbA1c patients subgroup.

BDI-II results will be also summarized by the mildly depressive patients subgroup.

Bone markers will also be summarized over the menopausal status subgroups. Serum osteocalcin will additionally be summarized by the low serum osteocalcin patients subgroup.

HPA axis markers will also be summarized over the etiology subgroups.

Select efficacy assessments including plasma ACTH, serum cortisol, late-night salivary cortisol, 24-hour UFC with creatinine, fructosamine, HbA1c, and serum osteocalcin will be summarized by the etiology and Cushing syndrome comorbidity subgroups by visit, Group 1, and Group 2. The adrenal etiology subgroup summaries will only be produced if there is a sufficient number of patients with post-baseline data.

Menstrual cycle will be summarized for all females by Group 1 and Group 2, and by the number and percentage of patients who have had vaginal bleeding since the last visit, summary statistics including change from baseline for duration of vaginal bleeding (days) and number of tampons/pads used per day, and frequency counts and percentages for vaginal flow (spotting, light, etc.).

Select efficacy assessments of plasma ACTH, 24-hour UFC with creatinine, fructosamine, HbA1c, osteocalcin, total cholesterol, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, triglycerides, estradiol (females only), testosterone (males only), and thyroid-stimulating hormone, with results classified as "low," "normal," or "high" with respect to parameter-specific reference ranges (ie, below the lower limit of the normal range, within the normal range, or above the upper limit of the normal range) will be summarized in the following three-by-three contingency tables:

- Shift from baseline to the worst observed post-baseline value within the treatment period per patient in each group;
- Shift from baseline to worst post-baseline value at each dose level per group;
- Shift from baseline to last post-baseline value at each dose level per group; and
- Shift from baseline to the last observed value within the treatment period per patient in each group.

Summary results will include the count and percentage of patients within each shift category in Group 1 and Group 2, and will be summarized over the etiology subgroups.

Similar to the responder analyses in the key efficacy endpoints, sensitivity responder analyses will be performed on patients in the IGT subgroup using the following criteria:

1. A patient is considered a responder if the patient's post-baseline HbA1c has decreased by $\geq 0.5\%$.
2. A patient is considered a responder at each visit if the patient's post-baseline 2-hour oGTT plasma glucose is normalized (< 7.8 mmol/L) or decreased by ≥ 2.8 mmol/L compared to baseline.
3. A patient is considered a responder if the patient's total daily insulin dose has decreased by $\geq 25\%$ or total daily sulfonylurea dose has decreased from baseline by $\geq 50\%$ and post-baseline HbA1c is unchanged or decreased compared to baseline.
4. A patient is considered a responder if at least one of the above criteria is met.

Sensitivity responder analyses will additionally be performed using the above criteria for #2 with the added requirement that a patient is only considered a responder once the patient reaches the responder critera and continues to meet the criteria throughout any

remaining post-baseline visits. Nonresponder rules, as described in Section 7.6.3.1, apply to the sensitivity responder analysis described in #2.

A histogram of mean serum osteocalcin (μg/L) will be presented by visit, Group 1, and Group 2, and will be repeated by the low serum osteocalcin subgroup. Plots of mean HbA1c, fructosamine, BDI-II total score, CushingQOL total score, and serum cortisol will be presented over time by Group 1 and Group 2. Plots of mean 24-hour UFC with creatinine and plasma ACTH will be presented over time by Group 1 and Group 2, and will be repeated by the etiology subgroups. Plots of plasma ACTH and serum cortisol will additionally be presented over all patients combined.

7.6.5 Statistical/Analytical Issues

7.6.5.1 Handling of Dropouts or Missing Data

In the key efficacy endpoint analyses, missing data will be primarily handled as follows:

- For the responder analyses, patients with missing data will be considered non-responders.
- For calculations involving AUC, including oGTT plasma glucose and insulin, the following rules for handling missing data will be applied:
    - If the pre-glucose drink time point and 30 minute post-glucose drink time point are missing, no AUC calculation will be performed. The AUC for that visit will be counted as missing.
    - If more than one post-glucose drink time points are missing, no AUC calculation will be performed.
    - If only one post-glucose drink time point is missing, and it is not the 30 minute post-glucose drink time point, then the AUC will be calculated with using available data. For example, if the 90 minute time point is missing, a larger trapezoid will be constructed to connect the 60 minute and 120 minute time points.
    - If only the 120 minute post-glucose drink time point is missing, the AUC will be calculated using the available data and AUC, and that AUC pre-glucose drink to 90 minute post-glucose drink value will be used in the summary tables.
- For the analyses using an MMRM, the F-tests will be based on the Kenward-Roger adjusted degrees of freedom to account for any missing data.
- Otherwise, observed values only will be used.

As a sensitivity approach to missing values for the key efficacy endpoints (including $AUC_{glucose}$ and $AUC_{insulin}$), missing data will be imputed as follows:

- For patients who did not adhere to protocol-defined dose escalation, missing data at a post-baseline visit will be imputed as the median of the non-missing values at that visit among patients who also did not adhere to protocol-defined dose escalation; and

- For patients who did adhere to protocol-defined dose escalation, missing data at a post-baseline visit will be imputed as the median of the non-missing values at that visit among patients who also adhered to protocol-defined dose escalation.

The above imputation will be applied by Group 1 and Group 2.

Patients who did not adhere to protocol-defined dose escalation include all patients who at any point during the study did not escalate dose at a dose-escalation visit, or experienced a dose reduction or dose interruption.

All efficacy by-visit analyses will include summaries for the following:

- Observed cases only, where no imputations will be used, except for the AUC missing data handling rules as described above; and

- The last observed value used in visit windowing (Section 7.1.2) prior to follow-up per patient. For patients who do not reach the last scheduled visit per protocol, the last observed value per patient is carried forward, effectively mimicking a last observation carried forward (LOCF) imputation.

7.6.5.2 Interim Analyses and Data Monitoring

As outlined in Section 6.1, an independent DRC will convene to review safety and PK results to confirm, revise, or adjust the Group 2 dose levels. The dose levels approved by the DRC for Group 2 will be based on estimated CORT125134 exposures ($AUC_{0\text{-}24h}$) for dose levels of 250, 300, and 350 mg; those exposure estimates will be based on Group 1 results as well as on results of PK modeling. As supervised by the DRC, the final dose levels for Group 2 will provide a simulated total systemic exposure [redacted]

7.6.5.3 Multicenter Studies

This is a multicenter study with multiple sites expected to participate. Efficacy data collected from all study centers will be pooled for data analysis. The effect of study center on the efficacy analysis results may be explored post-hoc, as needed.

7.6.5.4 Multiple Comparisons/Multiplicity

There will be no adjustments for multiple comparisons in the efficacy analysis for this study.

7.6.5.5 Active-Control Studies Intended to Show Equivalence

This study does not include an active-control product and is not intended to demonstrate equivalence between any two drug products.

7.6.6 Plasma Concentrations and Pharmacokinetic Analysis

The details of the PK analysis will be outlined in a separate document.

7.7 Safety Analysis

All safety analyses will be performed on the Safety Population. Select safety analyses may also be performed on the mITT Population and the mPP Sensitivity Population. All safety summaries will be presented by Group 1, Group 2, and Overall.

All safety data will appear in by-patient data listings.

7.7.1 Extent of Exposure

The duration of exposure will be presented in days and calculated as the date of last dose of study drug minus the date of first dose of study drug, plus one. Total actual dose received (mg) will be calculated as the number of capsules taken per visit x 50 mg, summed across all visits per patient. Duration of exposure, total actual dose received (mg), and number of days at each dose level will be summarized using descriptive statistics.

The number of patients reaching first, second, and third (Group 2 only) dose escalation, highest dose level received (eg, 150 to 400 mg), and the number of patients exposed at each dose level will be summarized by frequency counts and percentages across Group 1 and Group 2.

7.7.2 Adverse Events

Treatment-emergent adverse events are defined as those AEs with onset after the first dose of study drug or existing events that worsened after the first dose during the study and up to 28 days after the last dose of study drug. Treatment-emergent AEs will be summarized by group and displayed by dose level at AE onset, follow-up period if AE onset is after last dose of study drug, and overall, unless otherwise specified. Events reported with a partial onset date (eg, month and year are reported but the day is missing) will be considered to be treatment-emergent if it cannot be confirmed that the event onset was prior to the first dose of study drug based on the available date entries.

Verbatim terms on case report forms will be mapped to preferred terms and system organ classes using MedDRA, version 19.0.

Summaries that are displayed by system organ class and preferred terms will be ordered by descending incidence of system organ class and preferred term within each system

organ class. Summaries displayed by preferred term only will be ordered by descending incidence of preferred term. Summaries of the following types will be presented:

- Overall summary of number of unique TEAEs and treatment-emergent SAEs and patient incidence of TEAEs meeting various criteria;
- Patient incidence and total number of TEAEs by MedDRA preferred term by Group 1, Group 2, and Overall;
- Patient incidence and total number of TEAEs by MedDRA preferred term occurring in at least 10% of the population by Group 1, Group 2, and Overall;
- Patient incidence of TEAEs by MedDRA system organ class and preferred term;
- Patient incidence of TEAEs by CTCAE grade, MedDRA system organ class, and preferred term;
- Patient incidence of TEAEs by relationship to study drug, MedDRA system organ class, and preferred term;
- Patient incidence of severe (≥ CTCAE grade 3) TEAEs by MedDRA system organ class and preferred term;
- Patient incidence of severe (≥ CTCAE grade 3) TEAEs related to study drug by MedDRA system organ class and preferred term;
- Patient incidence of treatment-emergent SAEs by MedDRA system organ class and preferred term; and
- Patient incidence of AEs during Screening by MedDRA system organ class and preferred term.

At each level of summarization (eg, any AE, system organ class, and preferred term), patients experiencing more than one AE will be counted only once within each dose level or follow-up period. In the summary of TEAEs by severity grade, patients will be counted once at the highest severity reported at each level of summarization; in the summary of TEAEs by relationship, patients will be counted once at the closest relationship to study drug.

A swimmer plot of patient incidence of TEAEs occurring in at least 10% of the population by CTCAE grade and MedDRA preferred term will be presented by Group 1 and Group 2.

Adverse event data will be presented in data listings by group, patient, and event. Serious AEs, AEs leading to discontinuation of the study drug, and TEAEs with CTCAE greater than or equal to grade 3 will be presented in separate data listings.

7.7.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

All deaths during the study, including the post-treatment follow-up period, will be listed by patient, and will include the primary cause of death. Serious AEs and other significant AEs, including those that led to withdrawal, interruption, or dose reduction of the study drug, will be provided in separate patient data listings.

7.7.4 Clinical Laboratory Evaluation

All descriptive summaries of laboratory results will be based on data analyzed by the central laboratory and presented in Système International (SI) units, as suggested by the Center for Biologics Evaluation and Research and the Center for Drug Evaluation and Research *Position on Use of SI Units for Lab Tests* (Oct 2013). All data will be included in by-patient data listings. Laboratory measurements identified as abnormal (ie, outside the normal range) will also be listed separately by patient, study visit, dose at time of study visit, laboratory test, and unit.

Clinical laboratory measurements, including serum chemistry and hematology, will be summarized. Descriptive statistics will be presented for observed values and changes from baseline to the last post-baseline value within each dose level and follow-up period.

Where applicable, laboratory results will be classified as "low," "normal," or "high" with respect to the parameter-specific reference ranges (ie, below the lower limit of the normal range, within the normal range, or above the upper limit of the normal range). Three-by-three contingency tables will be presented for each laboratory parameter to summarize the following:

- Shift from baseline to the worst observed post-baseline value within the treatment period per patient;
- Shift from baseline to the last observed post-baseline value within each dose level per patient; and
- Shift from baseline to the last observed post-baseline value within the treatment period per patient.

Summary results will include the count and percentage of patients within each shift category.

Hematology and chemistry results for select parameters will be assigned a toxicity grade based on the U.S. Department of Health and Human Services *Common Terminology Criteria for Adverse Events (CTCAE)*, version 4.03 (Jun 2010), where applicable. Grades will be presented as none (Grade 0), mild (Grade 1), moderate (Grade 2), severe (Grade 3), or life-threatening (Grade 4). Death related to AE (ie, Grade 5) cannot be determined with available laboratory-based data collection and, thus, will not be summarized as a category. Summary tables will be presented for each laboratory parameter to summarize the following:

- The worst observed post-baseline CTCAE grade within each dose level and follow-up period per patient; and

- The last observed post-baseline CTCAE grade within each dose level and follow-up period per patient.

Summary results will include the count and percentage of patients within each dose level and follow-up period. A by-patient data listing for hematology and chemistry values with toxicity grade greater than or equal to Grade 3 will also be displayed.

Plots of mean values for ALT, AST, alkaline phosphatase, potassium, platelets, and absolute and total neutrophils will be presented by visit.

7.7.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

7.7.5.1 Vital Signs

Vital sign parameter measurements will be summarized. Descriptive statistics will be presented for results and change from baseline to the last post-baseline value within each dose level and follow-up period.

7.7.5.2 12-Lead Electrocardiogram

Twelve-Lead ECG interval parameters will be summarized. Descriptive statistics will be presented for results and change from baseline to the last post-baseline visit within each dose level and follow-up period using the average of the triplicate readings per patient per visit.

Twelve-lead ECG results will be classified by the investigator as “normal” and “abnormal.” A two-by-two contingency table will be presented to summarize the shift from the baseline category to the worst post-baseline category within the treatment period. Summary results will include the count and percentage of subjects within each shift category.

7.7.5.3 Physical Examination

Results of the physical examination will be presented in patient data listings by Group 1 and Group 2, patient, study visit, dose at time of study visit, and body system.

7.7.5.4 Pregnancy Tests

Results of the pregnancy tests will be presented in patient data listings by Group 1 and Group 2, patient, study visit, and dose at time of study visit.

7.7.5.5 Prior and Concomitant Medications

Medications will be coded using the World Health Organization (WHO Drug version 161E, enhanced) dictionary. Medications entered on the eCRF will be mapped to ATC drug class (level 4) and drug name.

Prior and concomitant medications will be summarized separately, and the study phase of each medication (if the medication is prior and/or concomitant) will be determined programmatically based on medication start and end dates. A prior medication is defined as any medication administered prior to the date of the first dose of study drug. A concomitant medication is defined as any medication administered on or after the date of the first dose of study drug. A medication may be defined as both prior and concomitant. If it cannot be determined whether a medication was received prior to the start of study drug dosing due to partial or missing medication start and/or end dates, it will be considered a prior medication. Likewise, if it cannot be determined whether a medication was received after the start of study drug dosing, it will be considered concomitant.

For the prior medications table summary, the number and percentage of patients receiving any medication will be summarized by Group 1, Group 2, and all patients combined, as will the number and percentage receiving any medication by ATC drug class and generic drug name. For all concomitant medications table summaries, the number and percentage of patients receiving any medication will be summarized by study drug dose category, follow-up period, Group 1, Group 2, and all patients combined, as will the number and percentage receiving any medication by ATC drug class and generic drug name. The study drug dose category or follow-up period each concomitant medication is assigned to will be determined by the medication start date. Patients reporting use of more than one medication at each level of summarization (any medication received, ATC class, and generic drug name) will be counted only once. ATC class terms will be displayed by descending order of incidence, as will generic drug names within each ATC class. The study phase during which each medication was received (eg, prior, concomitant, or both) will be presented on the listing of prior and concomitant medications.

Concomitant medications will also be summarized by the following:

- Medications used in greater than or equal to 20% of the patients in the Safety Population; and

- Medications used to treat diabetes or hypertension for patients in the Safety Population.

Tables summarizing reduction in antidiabetic and antihypertensive concomitant medications will also be presented by Group 1 and Group 2, and will include the number of patients taking the medication at baseline, median total daily dose at baseline, number of patients with a dose reduction, median reduction in total daily dose at last visit, and the number of patients with ≥ 50% reduction in daily dose.

Prior and concomitant medications will be presented in a by-patient data listing by Group 1 and Group 2, patient, ATC class and generic drug names, medication start date, and study drug dose level at time of medication start date. Concomitant medication will additionally be listed by Group 1 and Group 2, patient, medication group (antihypertensive or antidiabetic), week on study, total daily dose, dose change from baseline, and trough plasma concentration of CORT125134.

7.8 Patient Profiles

Individual patient profiles will be generated for all patients in the Safety Population, and will include graphical displays of the following: oGTT plasma glucose (mmol/L), mean 24-hour ambulatory systolic and diastolic BP (mmHg), mean nighttime 24-hour ambulatory systolic and diastolic BP (mmHg), mean daytime 24-hour ambulatory systolic and diastolic BP (mmHg), fructosamine (µmol/L), HbA1c (%), 24-hour UFC with creatinine (mmol/L), serum cortisol (nmol/L), plasma ACTH (pmol/L), ALT (U/L), AST (U/L), waist circumference, BMI, potassium (mmol/L), BDI-II total score, and CushingQOL total score. Profiles will include data from each patients' entire time on study drug.

Please see Section 7.6.3.3.2 for definitions of daytime and nighttime 24-hour ambulatory BP.

7.9 Determination of Sample Size

The study is not powered for formal hypothesis testing. The Sponsor has deemed 30 patients (15 per dose group) as a sufficient number to evaluate efficacy and safety/tolerability.

7.10 Changes in the Conduct of the Study or Planned Analyses

The SAP supercedes the statistical methods described in the clinical study protocol. Analysis methods that summarize and evaluate study efficacy endpoints for statistical significance will be implemented as described in the SAP.

8 REFERENCE LIST

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