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

NCT number: NCT02804750

Date: 15 January 2018

CLINICAL STUDY PROTOCOL CORT125134-451

Protocol Title	**Phase 2 Study of the Safety and Efficacy of CORT125134 in the Treatment of Endogenous Cushing's Syndrome**
Study Phase	2
IND Number	128625
Investigational Product	CORT125134
International Nonproprietary Name	Relacorilant
Medical Monitor	[redacted]
Clinical Trial Lead	[redacted]
Sponsor	Corcept Therapeutics Incorporated 149 Commonwealth Drive Menlo Park, California 94025 US +1 (650) 327-3270
Version	7.0
Date Final	15 January 2018

Good Clinical Practice Statement

This study will be conducted in accordance with Good Clinical Practice (GCP) as defined in International Conference on Harmonisation (ICH) guidelines and US Code of Federal Regulations Title 21, Parts 11, 50, 54, 56, 312, and Title 45 Parts 46, 160 and 164; the ICH document "Guidance for Industry – E6 Good Clinical Practice: Consolidated Guidance"; the EU Directives 2001/20/EC and 2005/28/EC; the Declaration of Helsinki (version as currently endorsed by the European Medicines Evaluation Agency and the United States Food and Drug Administration [FDA], 1989); Institutional Review Board (IRB) Guidelines; and applicable local legal and regulatory requirements.

Confidentiality Statement

SPONSOR SIGNATURE PAGE

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APPROVAL STATEMENT

The undersigned have reviewed the format and content of the above protocol and approved for issuance.

Signed:

[redacted]

Date

INVESTIGATOR SIGNATURE PAGE

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INVESTIGATOR AGREEMENT

By my signature below, I attest to the following:

1. I have read the attached protocol.
2. I agree to conduct the study as outlined in the protocol and in accordance with all applicable regulations and guidelines, including the Declaration of Helsinki (version as currently endorsed by the European Medicines Evaluation Agency and the United States Food and Drug Administration [FDA]); the principles of Good Clinical Practice (GCP) as described in the United States Code of Federal Regulations (CFR) – 21 CFR parts 50, 54, 56, and 312 and the ICH document "Guideline for Good Clinical Practice, E6 (R1)" dated 10 June 1996. Further, I will conduct the study in keeping with local legal and regulatory requirements.
3. I will initiate this study only with written and dated approval from the appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC). I understand that any changes in the protocol must be approved in writing by the Sponsor, the IRB/IEC, and, in certain cases the FDA or other applicable regulatory agencies, before they can be implemented.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Signed:

Signature	Date
Name	Institution

PROTOCOL SYNOPSIS

Name of Sponsor Corcept Therapeutics	**Name of Active Ingredient** CORT125134	**Study Number** CORT125134-451
Title of Study: Phase 2 Study of the Safety and Efficacy of CORT125134 in the Treatment of Endogenous Cushing's Syndrome		
Study centers: Multicenter (United States [US] and Europe)		
Study Period: Up to 38 weeks, including up to 6 weeks for screening, up to 28 weeks of treatment, and 4 weeks of follow-up	**Phase of Development:** Phase 2	
Study Rationale: CORT125134 (relacorilant) is a potent, selective glucocorticoid receptor (GR) antagonist being developed for the treatment of Cushing's syndrome. Glucocorticoid receptor antagonism is a proven mechanism of action for the treatment of the hyperglycemia secondary to hypercortisolism in adult patients with Cushing's syndrome. Since its mechanism of action is similar to that of mifepristone, with the exception that it does not bind the progesterone receptor, CORT125134 may be a treatment of Cushing's syndrome without the drawbacks of progesterone receptor antagonism.		
Objectives: The primary objective of the study is to assess the safety of CORT125134 in patients with endogenous Cushing's syndrome. The secondary objective of the study is to assess the evidence of reduction in cortisol activity following treatment with CORT125134 in patients with endogenous Cushing's syndrome based on improvement in blood glucose control and/or blood pressure (BP).		
Study Design and Methodology: This is a Phase 2, open-label study with two dose groups (15 patients/group), each with a two-step dose escalation. Because the study drug formulation has been updated (to enhance stability) for this protocol and has a different exposure/dose relationship than the formulation used in the initial Phase 1 Study CORT125134-120, full steady-state PK profiles will be generated at every dose level 2 weeks following the initial dose and each dose escalation. [redacted]		

- [redacted]

[redacted]

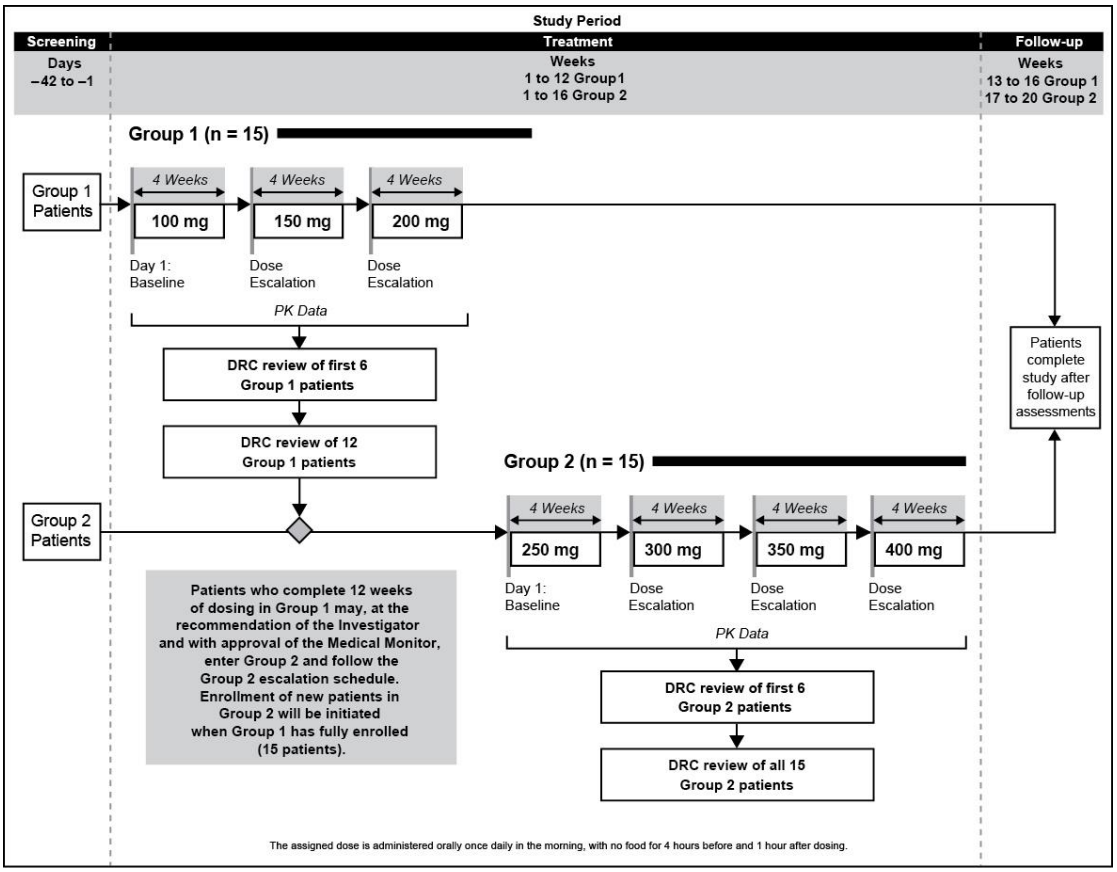
[redacted]

Enrollment of new patients in Group 2 will be initiated once Group 1 (15 patients) has fully enrolled.

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

period. Patients from Group 1 who roll over to Group 2 will follow the visit schedule for Group 2 without dose interruption. Patient dosing will be done at home, except on days of study visits.

All patients will undergo at least a two-step dose escalation unless the Investigator and Medical Monitor agree it is not advised because of safety or tolerability issues, or the Medical Monitor does not approve dose escalation based on the most recent PK results.



Number of Patients:

Approximately 30 patients will be enrolled in the study.

Patient Selection:

Approximately 30 male and female adults with a confirmed diagnosis of endogenous Cushing's syndrome and at least one of the following will be enrolled in this study:

- Type 2 diabetes or impaired glucose tolerance (at least 6 patients in both Group 1 and Group 2)
- Uncontrolled or untreated hypertension (at least 6 patients in both Group 1 and Group 2)

Possible etiologies of Cushing's syndrome include Cushing's disease, ectopic adrenocorticotropic hormone (ACTH)-secreting tumors, ectopic corticotropin-releasing hormone-secreting tumors, adrenal cortisol-secreting adenomas, adrenocortical carcinoma, primary pigmented nodular adrenal disease (PPNAD), or primary macronodular adrenal hyperplasia (PMAH).

Patients will be categorized in the impaired glucose tolerance/diabetes subgroup or the hypertension subgroup; a patient may be in both of these subgroups.

Inclusion Criteria:

Patients must meet all of the following inclusion criteria before study entry to be eligible for enrollment into the study:

1. Is a male or female adult, 18–80 years of age
2. Has a diagnosis of endogenous Cushing's syndrome confirmed by:
   At least two of the following test criteria (Nieman 2008):
   - Urinary free cortisol above the upper limit of normal (ULN) (50.0 µg/24 h) in at least 2, and up to 4, complete 24-hour collections within 3 weeks prior to Day 1 (baseline)
   - Late-night salivary cortisol above the ULN (at least 2, and up to 4, collections using a salivette) within 3 weeks prior to Day 1 (baseline)
   - Lack of cortisol suppression (>1.8 µg/dL serum cortisol) on either 1-mg overnight or 2-mg 48-hour dexamethasone suppression testing during screening or within 12 weeks before the ICF is signed.

   And

   At least two of the following clinical signs and symptoms of Cushing's syndrome:
   - Facial characteristics of a Cushingoid appearance (moon facies, dorsocervical fat pad, plethora)
   - Increased body weight or central obesity
   - Proximal muscle weakness
   - Low bone mass (dual energy X-ray absorptiometry [DXA] T < −1.0)
   - Psychiatric symptoms (including depression or psychosis)
   - Hirsutism and/or violaceous striae and/or acne
   - Easy bruising

   A patient with an adrenal lesion may alternatively qualify if there is autonomous cortisol secretion based on dexamethasone suppression testing (Fassnacht 2016) and supporting evidence of clinically significant cortisol excess. Such a patient must have:
   - Radiologically proven unilateral or bilateral adrenal disease (nodules, hyperplasia)
   - Lack of cortisol suppression (>5 µg/dL serum cortisol) on either 1-mg overnight or 2-mg 48-hour dexamethasone suppression testing during screening
   - Low or suppressed ACTH (<10 pg/mL) to confirm ACTH-independency
   - Presence of at least two comorbidities potentially related to cortisol excess (eg, type 2 diabetes, hypertension, obesity, osteoporosis), of which at least one is inadequately controlled by medical measures
3. Requires medical treatment of hypercortisolemia (ie, those for whom surgery or radiation is contraindicated or has been refused)
   Examples include, but are not limited to, patients with Cushing's disease who are post-surgery and/or post-radiation for whom additional surgery is not recommended; de novo patients with Cushing's disease who are not eligible for surgery due to comorbidities; and patients with ectopic ACTH-dependent Cushing's syndrome in which the tumor cannot be localized or completely removed.
4. Meets at least one of the following criteria:
   - Has type 2 diabetes mellitus as confirmed at screening visit with a fasting glucose >126 mg/dL and a 2-hour oral glucose tolerance test (oGTT) result for plasma glucose ≥200 mg/dL at 2 hours (Standards of Medical Care in Diabetes – 2015)
   - Has impaired glucose tolerance (2-hour oGTT result for plasma glucose in the range of ≥140 mg/dL to <200 mg/dL) (Standards of Medical Care in Diabetes – 2015)

- Has hypertension (mean systolic BP of 130–170 mmHg and/or a mean diastolic BP of 85–110 mmHg) based on 24-hour ambulatory BP measurement (O'Brien 2013)

5. If taking antidiabetic medication, is on a stable dose (ie, cannot start new medication or change dose within 4 weeks prior to the first dose of study drug)
6. If taking antihypertensive medication, is on a stable dose (ie, cannot start new medication or change dose within 4 weeks prior to the screening ambulatory BP measurement)
7. Has potassium within the normal range (3.5–5.3 mEq/L) at screening or corrected to within the normal range by Day 1
8. Female patients of childbearing potential must be willing to use a highly effective method of contraception from 30 days prior to Day 1 until 30 days after the last dose of study drug. Male patients with a female partner must agree to 2 forms of contraception, one of which must be a double-barrier method, from Day 1 until 30 days after the last dose of study drug. Highly effective methods of contraception include abstinence, oral contraceptives combined with a barrier method, diaphragm with vaginal spermicide, intrauterine device, condom and partner using vaginal spermicide, and surgical sterilization (≥6 months postsurgery).
9. (Female patients): Has a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline (Day 1)
10. Has a life expectancy of at least 6 months
11. Is able to participate in the study for up to 22 weeks in Group 1 and 26 weeks in Group 2, including returning to the investigative site to fulfill the safety and efficacy evaluations outlined in the protocol
12. Is able to read and understand the consent form and communicate with the study staff
13. Provides written consent to participate in the study prior to any study procedures and understands that he/she is free to withdraw from the study at any time

Exclusion Criteria:

Patients who meet any of the following exclusion criteria will not be eligible to participate in the study:

1. Has a non-endogenous source of hypercortisolemia
2. Has pseudo-Cushing's syndrome. Patients with known or suspected pseudo-Cushing's syndrome based on medical history (such as patients with severe obesity, major depression, or a history of alcoholism) should undergo a dexamethasone-CRH/DDAVP stimulation test (Yanovski 1993, Giraldi 2007, Yanovski 1998) to rule-in or rule-out this possibility.
3. Has uncontrolled, clinically significant hypothyroidism or hyperthyroidism
4. Has poorly controlled hypertension, defined as systolic BP >170 mmHg or diastolic BP >110 mmHg at screening
5. Has Stage ≥4 renal failure (ie, glomerular filtration rate ≤29 mL/min)
6. Has elevated total bilirubin >1.5×ULN or elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3×ULN
7. For patients with diabetes or abnormal oGTT at screening: has glycated hemoglobin (HbA1c) of >12% within 3 months of first dose of study drug
8. Has a screening hemoglobin level of <9 g/dL
9. Has a clinically significant electrocardiogram (ECG) abnormality at screening, which, in the opinion of the Investigator, will make the patient an unsuitable candidate for the study

10. Has a confirmed screening QTcF interval >450 ms for males and >470 ms for females (using Fridericia's correction) in the presence of a normal QRS interval (QRS <120 ms) or a history of additional risk factors for torsades de pointes
11. Is currently receiving chemotherapy for a tumor related to Cushing's syndrome
12. Had radiation therapy for Cushing's syndrome-related tumor within 1 year of screening period
13. Is planning surgery or radiation therapy for Cushing's syndrome-related tumor during the study
14. Has used or plans to use any of the following treatments for Cushing's syndrome, as specified:
    - Adrenostatic medications: metyrapone, ketoconazole, fluconazole, aminoglutethimide, or etomidate from 4 weeks prior to baseline (Day 1) through the follow-up visit
    - Adrenolytic medications:
      - In Group 1, any patients taking mitotane
      - In Group 2 only, patients with adrenocortical carcinomas taking mitotane whose dose has not been stable for at least 2 months prior to baseline (Day 1) or in whom increases in the mitotane dosage are expected through the end of dosing
    - Neuromodulator drugs that act at the hypothalamic-pituitary level: serotonin antagonists (cyproheptadine, ketanserin, ritanserin), dopamine agonists (bromocriptine, cabergoline), gamma-aminobutyric acid agonists (sodium valproate), and somatostatin receptor ligands (octreotide long-acting release [LAR], pasireotide LAR, lanreotide) from 8 weeks before baseline (Day 1) through the follow-up visit. Use of short-acting somatostatin analogs (octreotide, pasireotide) from 4 weeks prior to baseline (Day 1) through the follow-up visit.
    - Mifepristone, from 6 weeks before baseline (Day 1) through the follow-up visit
15. Has started or increased (or plans to start or increase) the dose of an antidepressant medication (eg, selective serotonin reuptake inhibitors or tricyclic compound) from 6 weeks before baseline (Day 1) through the end of the study dosing period
16. Has started or increased (or plans to start or increase) the dose of a lipid-lowering drug from 4 weeks before baseline (Day 1) through the follow-up visit
17. Is lactating
18. Has an acute or unstable medical problem that could be aggravated by treatment with the investigational study drug
19. Has a history of hypersensitivity or severe reaction to the study drug, to a similar class of drug, or to the study drug's excipients
20. Has taken any investigational drug within 30 days before baseline (Day 1), or within a period of less than five times the drug's half-life, whichever is longer
21. In the Investigator's opinion, should not participate in the study or may not be capable of following the study schedule
22. Has known HIV or hepatitis B or C infection
23. Is a family member of one of the Sponsor's employees, the Investigator, or the site staff directly working on the study

Test Product, Dose and Mode of Administration:

CORT125134, administered to fasting patients orally as capsules containing 50 mg of CORT125134:

Group 1: 100 mg/day for 4 weeks, then 150 mg/day for 4 weeks, then 200 mg/day for 4 weeks

Group 2: 250 mg/day for 4 weeks, then 300 mg/day for 4 weeks, then 350 mg/day for 4 weeks, then 400 mg/day for 4 weeks

Duration of Treatment: Up to 28 weeks

Criteria for Evaluation:

Key efficacy assessments

- Oral glucose tolerance test (impaired glucose tolerance/diabetes subgroup only)
- Ambulatory BP measurement (hypertension subgroup only)

Exploratory efficacy assessments

- Physician's Global Assessment
- HbA1c
- Fructosamine
- Adiponectin
- 24-hour urinary free cortisol (UFC) with creatinine
- Late-night salivary cortisol
- Body weight, waist circumference
- Beck Depression Inventory (BDI-II), Trail Making Test, CushingQoL
- Lipid panel
- Sit-to-stand test
- Sex hormone levels
- Menstrual cycle characterization (premenopausal women not on hormonal birth control)
- Coagulation tests
- Glucocorticoid receptor (GR) biomarker tests
- Bone markers (serum bone alkaline phosphatase, osteocalcin, urine N-telopeptides of type 1 collagen [NTx], calcium from 24-hour UFC)
- Hypothalamic-pituitary-adrenal (HPA) axis markers, including plasma ACTH and serum cortisol concentrations
- ACTH precursors
- High-sensitivity C-reactive protein concentrations
- 24-hour urine calcium and sodium
- Insulin-like growth factor (IGF-1)
- Thyroid function tests

Pharmacokinetics

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/early termination (ET) for patients in Group 1.

For patients in Group 2, 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/early termination (ET).

Safety

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

Statistical Methods

The sample size is not intended to support formal hypothesis testing.

All summaries will be presented by starting dose group, regardless of the actual dose level at the time point associated with the data collection. In addition, data will be tabulated for all patients combined.

In general, continuous variables will be summarized by the number of patients with non-missing data, mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized by the number and percentage of patients in each category.

The analysis population for all efficacy and safety analyses will include all patients who received at least one dose of study drug. The PK analysis population will comprise all patients who have evaluable PK data. For all analyses, the patient will be included in the dose group to which he or she was assigned, regardless of actual dose level at the time point when the data were collected.

Select efficacy endpoints will be analyzed by subgroup only:

- Patients with impaired glucose tolerance/diabetes
- Patients with hypertension.

All enrolled patients will belong to at least one of these subgroups and an individual patient may be included in both. If a patient enters the study with hypertension but takes an additional antihypertensive medication or increases the dosage of a concurrent antihypertensive medication, that patient will be classified as a nonresponder. If a patient enters the study with diabetes/impaired glucose tolerance but takes an additional diabetes medication or increases the dosage of a concurrent diabetes medication, that patient will be classified as a nonresponder.

Diabetes/Impaired Glucose Tolerance Subgroup

The area under the concentration-time curve for glucose ($AUC_{glucose}$) will be calculated based on results of the oGTTs from baseline to Week 12/ET for Group 1 and Week 16/ET for Group 2, for those patients with impaired glucose tolerance or diabetes at study entry. A responder will be defined as a patient who experiences at least a 25% decrease from baseline in $AUC_{glucose}$. The number and percentage of patients who are responders will be presented by dose group and for all patients, along with the 95% binomial exact confidence interval.

$AUC_{glucose}$ will be summarized by descriptive statistics by dose group and for all patients. In addition, plasma glucose, HbA1c, and adiponectin concentrations will be summarized using descriptive statistics by visit, time point, and dose group, to include the change from baseline. Plots of the mean plasma glucose values over time will be presented.

The number and percentage of patients whose dose of medications that lower blood glucose decreased, stayed the same, or increased from baseline to Week 12/ET in Group 1 and Week 16/ET in Group 2 will be summarized, among those patients taking such medications at baseline.

Hypertension Subgroup

Changes in the mean diastolic and mean systolic BP measured by 24-hour ambulatory BP monitoring will be analyzed for patients with hypertension at study entry. A responder will be defined as a patient who experiences at least a 5 mmHg decrease in diastolic or systolic BP from baseline to Week 12/ET in Group 1 and Week 16/ET in Group 2. The number and percentage of patients who are responders will be presented by dose group and for all patients, along with the 95% binomial exact confidence interval.

Diastolic and systolic BP will be summarized using descriptive statistics by visit, time point, and dose group.

The number and percentage of patients whose dose of antihypertensive medication decreased, stayed the same, or increased from baseline to Week 12/ET in Group 1 and Week 16/ET in Group 2 will be summarized, among those patients taking such medications at baseline.

Safety

Adverse events will be mapped to system organ classes and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs (TEAEs) are defined as those that start or worsen after the start of study treatment and up to 28 days after the last dose of study treatment.

Treatment-emergent AEs will be summarized overall and by dose group and displayed by system organ class and preferred term. Treatment-emergent AEs will be further summarized by severity and relationship to study treatment. At each level of summation, patients will be counted only once, under the greatest severity and strongest study-drug relationship (as reported by the Investigator).

All AEs (whether TEAEs or not) will be listed by individual patient, including information regarding onset, duration, severity, and relationship to study drug. Serious AEs and AEs that led to withdrawal from the study will be listed by individual patient.

Clinical laboratory test results (chemistry and hematology), vital sign measurements, and ECG interval results will be summarized overall and for each dose group by parameter, visit, and time point using descriptive statistics, to include the change from baseline values. Shift tables will be constructed that describe changes from baseline to the end of treatment in clinical laboratory values.

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LIST OF ABBREVIATIONS WITH DEFINITIONS

ACTH	adrenocorticotropic hormone
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{0–24h}$	area under the concentration-time curve over 24 hours
$AUC_{glucose}$	area under the concentration-time curve for glucose
BDI-II	Beck Depression Inventory
BP	blood pressure
Ca	calcium
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DHEA-S	dehydroepiandrosterone sulfate
DXA	dual energy X-ray absorptiometry
EAS	ectopic ACTH secretion
ECG	electrocardiogram
eCRF	electronic case report form
ET	early termination
FKBP5	FK506 binding protein 5
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GR	glucocorticoid receptor
HbA1c	glycated hemoglobin
HEENT	head, eyes, ears, nose, throat
HPA	hypothalamic-pituitary-adrenal
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IGF	insulin-like growth factor
IND	Investigational New Drug
IRB	Institutional Review Board
Ki	inhibition constant
LAR	long-acting release

MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
Na	sodium
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect-level
NTx	N-telopeptides of type 1 collagen
oGTT	oral glucose tolerance test
PK	pharmacokinetic
PMAH	primary macronodular adrenal hyperplasia
PPNAD	primary pigmented nodular adrenocortical disease
RBC	red blood cell
SAE	serious adverse event
T3	triiodothyronine
T4	thyroxine
TAT	tyrosine amino transferase
TEAE	treatment-emergent adverse event
TNF-α	tumor necrosis factor alpha
UFC	urinary free cortisol
ULN	upper limit of normal
US	United States
WBC	white blood cell

1 INTRODUCTION

1.1 Background

In healthy individuals, cortisol is secreted from the cortical cells of the adrenal glands under the control of the pituitary hormone adrenocorticotropic hormone (ACTH). Endogenous Cushing's syndrome is a rare multisystem disorder that results from overproduction of the glucocorticoid hormone cortisol. In both adults and children, Cushing's syndrome is most commonly caused by an ACTH-secreting pituitary tumor (Cushing's disease). Other forms of Cushing's syndrome result from autonomous production of cortisol from adrenal cortical tumors or overproduction of ACTH from non-pituitary tumors (ectopic ACTH syndrome).

The only curative treatment is resection of the tumor source of the excess cortisol. Depending on the nature of the underlying tumor (ie, benign versus malignant, localized versus metastatic), the selected treatment may be surgery, radiotherapy, medical therapy, or a combination of these.

Pharmacological treatment is not curative in Cushing's syndrome–only successful surgery is–but it serves to control the disease after unsuccessful surgery or recurrence (Nieman 2015). It may also be used to lower cortisol activity to improve a patient's condition prior to surgery and is employed as interim therapy under specific circumstances, such as in patients waiting for radiotherapy to be effective (Cuevas-Ramos 2014).

Currently, there are two United States (US) Food and Drug Administration (FDA)-approved medical therapies for endogenous Cushing's syndrome. The first is mifepristone (Korlym®), which has been approved for the control of hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery. The second is pasireotide (Signifor®), a somatostatin receptor agonist, which has been approved for the treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative.

In the US, drugs commonly used off-label in the medical therapy of Cushing's syndrome either inhibit adrenal steroidogenesis (such as metyrapone, mitotane, or ketoconazole), or reduce ACTH release from the pituitary gland (such as the dopamine agonists bromocriptine and cabergoline; and the somatostatin receptor ligand octreotide). In general, the former agents show significant toxic effects and/or loss of efficacy over time, and the latter agents have not shown substantial efficacy. In Europe, drugs approved for the treatment of Cushing's syndrome include aminoglutethimide (Orimeten®), ketoconazole (Nizoral®), metyrapone (Metopirone®), mitotane (Lysodren®), and pasireotide (Signifor) (Eckstein 2014).

CORT125134 is a potent, selective glucocorticoid receptor (GR) antagonist being developed for the treatment of Cushing's syndrome. The mechanism of action of CORT125134 is similar to that of mifepristone, with the exception that CORT125134 does not bind to the progesterone receptor. The potential advantage of CORT125134 compared with mifepristone is its selective and potent GR antagonism, without anti-progesterone effects, including endometrial hypertrophy and the potential for irregular vaginal bleeding.

CORT125134 is a high-affinity antagonist of the GR (inhibition constant [Ki] <1 nM in a human GR binding assay and <10 nM in a human functional assay). Across a range of in vitro assays it is similar in both GR affinity and inhibition to mifepristone (an antagonist of both the

progesterone receptor and GR as measured in ligand binding assays), as summarized in Table 1. Functional antagonism is assessed by measuring the ability of CORT125134 and mifepristone to prevent dexamethasone-induced increase in the activity of tyrosine amino transferase (TAT). The expression of the TAT gene is regulated by GR, and a GR agonist such as dexamethasone increases gene expression, protein production, and enzyme activity. For routine screening, the human liver carcinoma cell line Hep-G2 and the rat hepatoma cell line H4-II-EC4 are used. Glucocorticoid receptor agonists also reduce the production of several inflammatory cytokines, including tumor necrosis factor alpha (TNF-α), in human peripheral blood mono-nuclear cells stimulated with lipopolysaccharide, by repressing gene transcription. Glucocorticoid receptor antagonists such as mifepristone and CORT125134 reverse the effects of the agonist dexamethasone.

Table 1 Inhibition Constants (Ki) for CORT125134 and Mifepristone in a Human Glucocorticoid Receptor Fluorescence Polarization (FP) Binding Assay and in Human Glucocorticoid Receptor Activation (TAT) and Repression (TNF-α) Assays

Compound	FP Binding Assay Ki (nM)	Functional GR (TAT) Ki (nM)		Functional GR (TNF-α) Ki (nM)
		Human HepG2	Rat H4-II-EC4	Human PBMC
CORT125134	0.15	7.2	1.2	9.1
Mifepristone	0.09	3.1	2.2	6.2
CORT125201*	0.20	7.6	Not tested	Not tested

*CORT125201 is a metabolite of CORT125134

1.1.1 Nonclinical Data

To characterize the nonclinical safety of CORT125134, preliminary ascending single-dose, repeat-dose, and Good Laboratory Practice (GLP) 14-day repeat-dose toxicology studies were conducted in rats and cynomologus monkeys. The results of the general toxicology studies indicated that CORT125134 produced many anticipated effects related to the antagonism of GR and compensatory perturbations of the hypothalamic-pituitary-adrenal (HPA) axis. In these studies, safety pharmacology assessments included cardiovascular effects in monkeys, respiratory function in rats, and neurobehavioral effects in rats. In general, there were no remarkable central nervous, respiratory, or cardiovascular system effects in rats or monkeys following single oral doses up to 200 mg/kg (highest dose tested). [redacted]

[redacted]

CORT125134 was not genotoxic in in vitro bacterial and mammalian cell assays or in vivo in the rat micronucleus assay.

CORT125134 is not a substrate for permeability glycoprotein (P-gp). It appears to be eliminated via multiple metabolic pathways including cytochrome P450 (CYP) 2C8, CYP3A4 and CYP3A5 and a non-CYP pathway but not via renal elimination. This is reassuring with respect to the risk of drug-drug interactions affecting exposure to CORT125134. Based on in vitro studies, CORT125134 appears to be a potent inhibitor of CYP3A4 and CYP2C8 and a modest inhibitor of CYP2C9, CYP2C19, CYP2D6 and CYP3A5. No significant induction of CYP1A2, CYP2B6 or CYP3A4 was noted in a study carried out in human hepatocytes.

More information is provided in the Investigator's Brochure

1.1.2 Clinical Experience: Safety

Clinical experience with CORT125134 is derived from three studies conducted in healthy subjects; Study CORT125134-120 which evaluated single ascending and multiple ascending doses of the earlier formulation in healthy subjects, Study CORT125134-122 which evaluated a single dose of 150 mg of the current formulation (modified to improve stability) in healthy subjects, and Study CORT125134-453 which evaluated multiple ascending doses of the current formulation in healthy subjects.

Study CORT125134-120 consisted of Part 1 and Parts 2 and 3, which assessed the safety, tolerability, and pharmacokinetics (PK) of single and multiple ascending doses, respectively, in healthy volunteers. In total across all single-dose groups in Part 1, 69 subjects received CORT125134 and 12 received placebo (8 subjects received each of 5, 15, and 50 mg fasted; 7 received 150 mg fasted; 6 received 300 mg fasted, and 24 received 500 mg fasted, and a further 8 received 150 mg fed). Across all multiple-dose groups in Part 2, 25 subjects received up to 14 days' treatment with CORT125134 and 9 received placebo (9 subjects received each of 50 and 150 mg, and 7 subjects received 250 mg once daily) after an overnight fast. Dosing in Part 3 of the study, in which the safety, tolerability and PK of a higher multiple dose (500 mg) daily in healthy volunteers were assessed, was terminated prematurely due to lack of tolerability (principally musculoskeletal complaints). Safety follow-up for Part 3 subjects is completed (refer to accompanying Investigator Brochure).

Overall, CORT125134 was safe and well tolerated following single doses up to 500 mg or repeated doses up to 250 mg once daily. The overall incidence of treatment-emergent adverse events (TEAEs) was low after administration of CORT125134, with no notable difference in the percentage of subjects reporting TEAEs after dosing with active drug compared with placebo.

In the multiple-ascending-dose study (Part 2), TEAEs in the musculoskeletal and connective tissue disorders system organ class were reported more frequently by subjects treated with CORT125134, and with increasing frequency with increasing dose. The proportions of subjects with reports of musculoskeletal and connective tissue disorder TEAEs by daily dose were Placebo: 0 subjects; 50 mg: 2 subjects (22.2%); 150 mg: 4 subjects (44.4%); and 250 mg: 4 subjects (57.1%). The events reported were coded as back pain, pain in extremity, myalgia, arthralgia, musculoskeletal pain, spinal osteoarthritis, and tendon discomfort. However, back pain (0% [0/9] placebo, 22.2% [2/9] 50 mg, 11.1% [1/9] 150 mg, and 28.6% [2/7] 250 mg), pain in extremity (0% [0/9] placebo, 0% [0/9] 50 mg, 11.1% [1/9] 150 mg, and 28.6% [2/7] 250 mg), and myalgia (0% [0/9] placebo, 0% [0/9] 50 mg, 22.2% [2/9] 150 mg, and 0% [0/7] 250 mg) were the only TEAEs reported for at least 2 subjects in any of the three multiple ascending dose cohorts. There was also some evidence that gastrointestinal TEAEs, such as abdominal pain upper, epigastric pain, nausea, vomiting, and constipation were reported with increasing frequency with dose of CORT125134, with the majority assessed as treatment-related following both single and multiple doses.

Most events were mild, but moderate abdominal pain and constipation in one subject treated with CORT125134, 250 mg daily, and severe pain in extremity in one subject treated with CORT125134, 150 mg daily, resulted in withdrawal of treatment.

Findings in Part 3, the multiple-ascending-dose extension cohort, show that CORT125134 500 mg once daily exceeds the maximum well-tolerated dose, with musculoskeletal symptoms and earache being the most frequently reported limiting symptoms.

One serious adverse event (SAE) was reported in this Phase 1 study. A subject treated with CORT125134, 50 mg daily was admitted to the hospital overnight due to a head injury during the follow-up period. The subject declared this was due to an accidental fall; however, the hospital record states that the subject was assaulted. The event was considered unrelated to study treatment and the subject made a full recovery.

There were no clinically significant findings in any laboratory assessments, vital signs, 12-lead ECGs, Holter electrocardiograms (ECGs), or body weight. Five CORT125134-treated subjects in the multiple-dose part of the study had substantial reductions in platelet count during the treatment period, with prompt recovery subsequently. The average of the absolute platelet counts decreased in the CORT125134-treated groups when compared with placebo. None of the individual decreases was considered clinically significant, and an independent review by an experienced hematologist did not consider these findings a safety concern.

Study CORT125134-122 evaluated the safety, tolerability, and PK of a single 150 mg dose of the CORT125134 current formulation in 8 healthy male volunteers. No serious or severe adverse events were reported during the study, and no subjects withdrew from the study due to adverse events. A total of 1 treatment-emergent adverse event (mild dizziness) was reported by 1 of 8 subjects (12.5%) during the study.

[redacted]

More information is provided in the Investigator's Brochure.

1.1.3 Clinical Experience: Pharmacokinetics

Pharmacokinetic results from the Phase 1 study (Study CORT125134-120) in healthy subjects demonstrated that CORT125134 concentrations declined in a multiphasic manner. Plasma concentrations appeared to plateau by Day 7 with little accumulation from Day 7 to Day 14, indicating that concentrations were likely at or near steady-state by Day 7. Concentrations declined to unmeasurable levels prior to or by the last sampling time point, indicating that the

concentration-time profile was completely captured within the planned sampling time window and was limited only by the lower limit of the bioanalytical method.

The half-life for CORT125134 in Part 2 after the last dose on Day 14 averaged 11.99, 19.09, and 14.71 hours at 50, 150, and 250 mg/day, respectively.

Based on the limited data available, an effect of food to reduce exposure to CORT125134 cannot be excluded.

Dose proportionality analysis showed that for both maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC), exposure increased in a greater than proportional manner with dose increment for both single and daily dosing. This effect was particularly noticeable at the lowest doses in the single ascending dose phase. Inter-subject variability in exposure was moderate.

[redacted]

Metabolite (CORT125201) exposure was low compared with parent drug. At presumed steady-state, metabolite AUC_{0-24h} was less than 5% that of parent drug.

In Study CORT125134-122, which evaluated the 150-mg dose of the updated, current capsule formulation in 8 healthy volunteers, CORT125134 was absorbed rapidly (median T_{max} 1 hour, range 1-2 hours) to a mean C_{max} of 200.5 ng/mL. Thereafter, elimination was rapid (median T_{last} 24 hours; mean $t_{½}$ 7.7 hours), giving a mean AUC_{inf} of 801 ng•h/mL.

In comparison of the current capsule formulation with historical data for the earlier capsule formulation, exposure from the current formulation was substantially lower, with C_{max} approximately 30 to 52% and AUC_{inf} 22 to 36% of that of the earlier formulation [redacted].

[redacted]

1.1.4 Clinical Experience: Pharmacodynamics

The PD effects of CORT125134 were assessed in Study CORT125134-120 by evaluating the ability of CORT125134 to prevent selected effects of the GR agonist prednisone. This evaluation was conducted after the administration of a single dose of CORT125134 (500 mg) in Part 1 of the study, and 14 days repeat dosing of CORT125134 (250 mg/day) in Part 2 of the study. In Part 1, a single dose of mifepristone (600 mg) was used as a comparator.

Administration of a single dose of prednisone (25 mg) resulted in a rapid drop in eosinophils, lymphocytes, and osteocalcin, and an increase in neutrophils. After administration of 600 mg mifepristone with 25 mg prednisone, the effect of prednisone on these parameters was ameliorated to a large extent. Similarly, after administration of 500 mg CORT125134 the effect

of prednisone was also ameliorated. The 24-hour AUC on time point deltas for proof of pharmaceutical effect (PoPE) parameters for both mifepristone and CORT125134 were significantly different from those for prednisone alone on Day −19 ($p < 0.05$) for eosinophils and neutrophils but not plasma osteocalcin. For lymphocyte 24-hour AUC, CORT125134 with prednisone (but not mifepristone with prednisone) was significantly different to prednisone alone.

Administration of a single dose of prednisone 25 mg resulted in an abnormal glucose tolerance test. After administration of 500 mg of CORT125134 with 25 mg of prednisone, the effect of prednisone on glucose tolerance appeared to be ameliorated. Administration of 600 mg of mifepristone with 25 mg of prednisone was used as comparator.

In Part 2 of the study, the 24-hour AUC on time point deltas for PoPE parameters for CORT125134 on Day 14 were significantly different from those for prednisone alone on Day −5 ($p < 0.05$) for eosinophils, neutrophils, and osteocalcin but not lymphocytes. Because there were only 3 placebo-treated subjects, no statistical comparison was done between placebo- and CORT125134-treated subjects. However, it was evident from plotting the data that active treatment on Day 14 resulted in an amelioration of the prednisone effect whereas placebo treatment did not.

The administration of prednisone increased FK506 binding protein 5 (FKBP5) mRNA expression, and this increase was prevented by co-administration of either mifepristone (600 mg) or CORT125134 (500 mg) with the prednisone in Part 1 of the study. After dosing with CORT125134 (250 mg) for 14 days in Part 2 of the study, prednisone did not induce FKBP5 mRNA expression. Administration of placebo for 14 days did not prevent prednisone-induced FKBP5 mRNA expression.

Due to inhibition of the negative feedback mechanism, the administration of a GR antagonist causes an increase in morning serum plasma cortisol levels. After administration of CORT125134 for 14 days, there appeared to be a dose-related effect, with increased cortisol levels at the higher doses. A comparison between morning cortisol levels on Day 13 for CORT125134-treated subjects with placebo-treated subjects showed that 50 mg CORT125134 did not have a statistically significant effect ($p = 0.2634$), whereas 150 mg and 250 mg CORT125134 did have a statistically significant effect ($p = 0.0025$ and 0.0006, respectively).

Analysis of ECG safety data from the Phase 1 study showed that CORT125134 at doses up to 500 mg, which resulted in plasma concentrations up to approximately 3 µg/mL, did not have a clinically relevant effect on ECG parameters (cardiac safety report, data on file). Based on the exposure-response analysis of the QT effect, the data demonstrated that CORT125134 does not have a clinically relevant effect on the QTc interval. An effect on ΔΔQTcF above 10 ms could clearly be excluded within the studied range of plasma concentrations up to approximately 3 µg/mL, which corresponded to single doses up to 500 mg or repeated doses up to 250 mg once daily.

1.1.5 Adverse Events with Similar Drugs

Mifepristone is a potent antagonist of both progesterone via the progesterone receptor and cortisol via the GR receptor, and has weak antiandrogenic activity. In the pivotal, uncontrolled, open-label, multicenter study of mifepristone in 50 patients with Cushing's syndrome, the

following adverse events (AEs), as reported in the Korlym prescribing information, were reported in ≥20% of patients: nausea, fatigue, headache, decreased blood potassium, arthralgia, vomiting, peripheral edema, hypertension, dizziness, decreased appetite, and endometrial hypertrophy. "Adrenal insufficiency" was reported in 2 patients (4%). The most common symptoms of adrenal insufficiency were nausea and decreased appetite. No hypotension or hypoglycemia was reported during the events. Adrenal insufficiency resolved in both cases with mifepristone interruption and/or dexamethasone administration. Adrenal insufficiency was reported in 5 of the 30 patients (16.7%) who participated in the extension study, in which patients received up to 1 year of treatment with mifepristone.

Across five psychotic depression trials that evaluated 7-day dosing with mifepristone (up to 1200-mg dose), AEs reported in ≥10% of patients who received mifepristone (N = 833) were nausea and headache. In these trials, the majority of reported treatment-emergent SAEs were psychiatric. The three most prevalent psychiatric disorder SAEs reported were worsened depression, worsened psychosis, and suicidal ideation. There were no reports of adrenal insufficiency.

1.2 Rationale for the Current Study

This will be the first prospective clinical study to evaluate the safety of CORT125134, a selective GR antagonist, in patients with endogenous Cushing's syndrome for whom the Investigator has determined that medical treatment of endogenous hypercortisolemia is indicated. The study will assess the effect of treatment on the signs and symptoms of hypercortisolemia.

Glucocorticoid receptor antagonism is a proven mechanism of action for the treatment of the hyperglycemia secondary to hypercortisolism in adult patients with Cushing's syndrome. Since its mechanism of action is similar to that of mifepristone, with the exception that it does not bind the progesterone receptor, CORT125134 may be a treatment of Cushing's syndrome without the drawbacks of progesterone receptor antagonism that may result in untoward reproductive effects and/or interruption of therapy.

The activity of CORT125134 has been demonstrated in various *in vitro* assays and CORT125134 was shown to be well tolerated in a Phase 1 study that examined the clinical PK and safety of CORT125134 doses as high as 350 mg for 14 days. The combination of the preclinical and clinical assessments justifies the evaluation of CORT125134 in patients with Cushing's syndrome.

The study is intended to demonstrate safety and clinical effects of GR antagonism, with an emphasis on blood glucose control and blood pressure (BP) control, in patients with Cushing's syndrome. The PK of CORT125134 will also be evaluated. In addition to blood glucose control and BP control, several other exploratory efficacy assessments will be used to assess clinical benefit. In patients with adrenal Cushing's syndrome, changes of the HPA axis will be monitored in addition to clinical monitoring. Successful GR blockade at the hypothalamus and pituitary level will reverse the excessive negative cortisol feedback, as shown by ACTH increase, indicating recovery of the HPA axis. In addition, increased production of adrenal androgens (androstenedione and dehydroepiandrosterone sulfate [DHEA-S]), which are regulated by ACTH, would also signal recovery of the atrophic adrenal tissue.

Changes in serum cortisol, late-night salivary cortisol, and urinary free cortisol (UFC) will also be evaluated, as well as changes in body weight, waist circumference, body composition, lipid levels, and hormone levels; effects on strength and menstrual cycle (premenopausal female patients not taking hormonal birth control); a quality-of-life assessment (CushingQoL); the Beck Depression Inventory (BDI-II); and a Physician's Global Assessment of the signs and symptoms of Cushing's syndrome.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2 STUDY OBJECTIVES

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

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

3 STUDY DESIGN

3.1 Overview of Study Design

This is a Phase 2, open-label study to evaluate the safety and efficacy of two dose regimens of CORT125134 in patients with endogenous Cushing's 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. The impaired glucose tolerance/diabetes subgroup will include at a least 6 patients in both Group 1 and Group 2. The hypertension subgroup will include at least 6 patients in both Group 1 and Group 2.

Approximately 30 patients will be enrolled across clinical sites in the US and Europe. Two dose groups including 15 patients per group will be evaluated, each with a two-step dose escalation. The study will consist of 3 periods: a screening period (Days −42 to −1); a treatment period consisting of 4 weeks at the initial dose, immediately followed by 4 weeks at the next higher dose (ie, first dose escalation), immediately followed by an additional 4 weeks at the next higher dose (ie, second dose escalation); and a follow-up period of 4 weeks.

Because the study drug formulation has been updated (to enhance stability) for this protocol, and has a different exposure/dose relationship than the formulation used in the initial Phase 1 Study CORT125134-120 [redacted], full steady-state PK profiles will be generated at every dose level 2 weeks following the initial dose and each dose escalation. The Medical Monitor must approve all individual dose escalations and will review the patient's safety profile and steady-state PK results, including $AUC_{0–24h}$ values. If the patient's projected $AUC_{0–24h}$ value meets the dose-escalation rules outlined in Section 5.4.2, the patient's dose will be escalated; otherwise, the patient's dose will remain at the current level.

An independent DRC will convene at least 4 times during the study to review safety and PK results, as listed below.

Two dose groups will each enroll 15 patients sequentially, with enrollment of the second dose group occurring after the 15th patient has enrolled in the first dose group, as follows:

- Patients enrolled into Group 1 will receive CORT125134 100 mg/day for 4 weeks, then CORT125134 150 mg/day for 4 weeks, then CORT125134 200 mg/day for 4 weeks.
- After 6 patients have received CORT125134 through Week 10 (ie, 2 weeks following dose escalation to 200 mg/day), the DRC will review PK and safety data to confirm the appropriateness of the dose levels in Group 1.
- After 12 patients have received CORT125134 through Week 10 (ie, 2 weeks following dose escalation to 200 mg/day), the DRC will review PK and safety data and recommend changes, if applicable, to the dose escalation in Group 2.
- Group 2: CORT125134 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. Patients who discontinue prior to Week 10 may be replaced to ensure that at least 12 patients provide serial PK data through Week 10 in Group 1 and Group 2.
- The DRC will also meet during Group 2, when steady-state PK data are available for 6 patients who have reached their highest CORT125134 dose (ie, Week 10 if 350 mg and Week 14 if 400 mg) and at the end of the study.

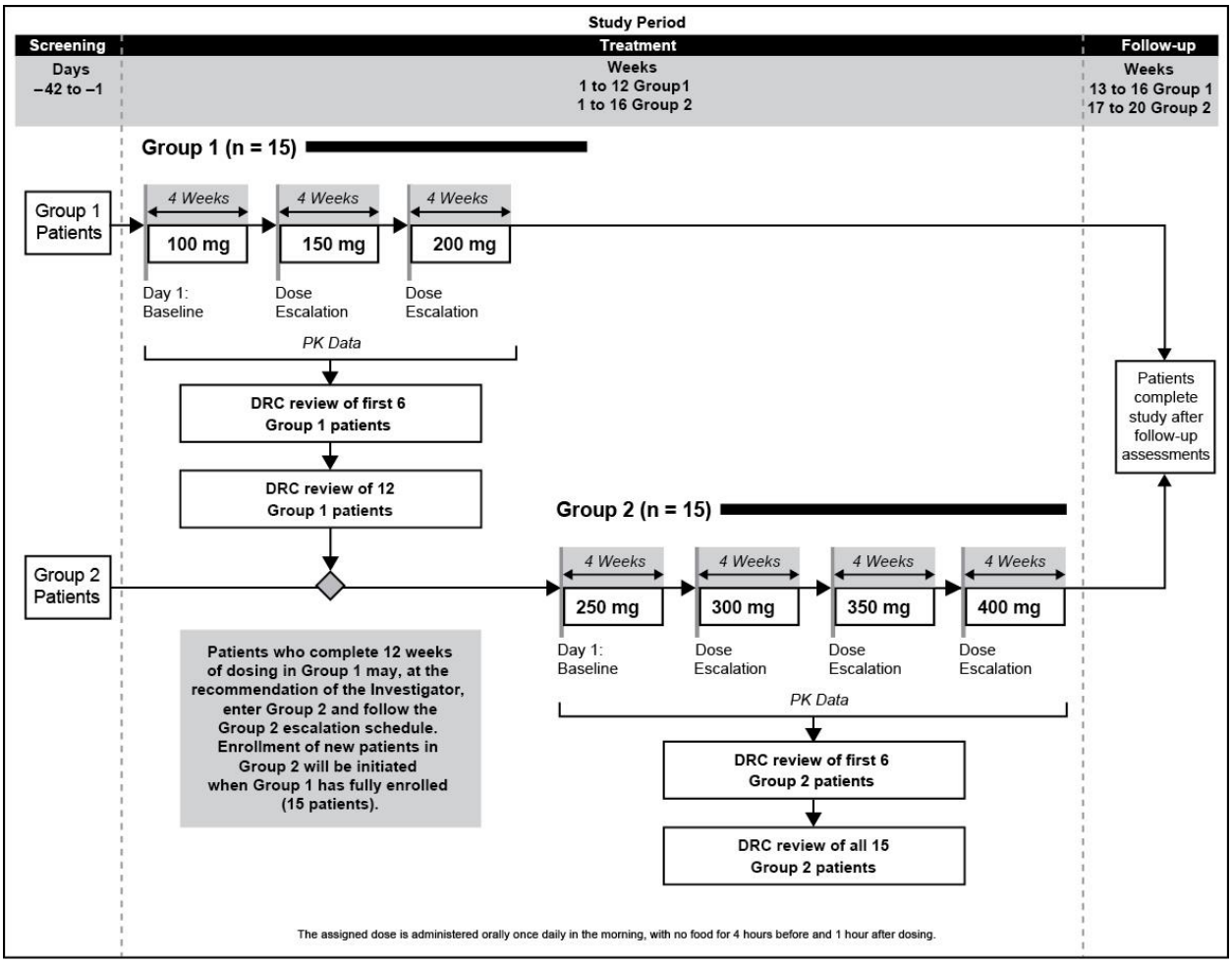
- In the event that patients enrolled in Group 2 cannot tolerate the starting dose, they will be allowed to continue on study at a lower dose level (ie, 150 or 200 mg).
- Patients who complete 12 weeks of dosing in Group 1 may, at the recommendation of the Investigator and with agreement of the Medical Monitor, roll over to Group 2 and follow the Group 2 dose escalation schedule.

Enrollment of new patients in Group 2 will be initiated once Group 1 (15 patients) has fully enrolled.

All patients will undergo at least a two-step dose escalation (Figure 2) unless the Investigator and Medical Monitor agree it is not advised because of safety or tolerability issues, or the Medical Monitor does not approve dose escalation based on the most recent PK results (see Section 5.4.2). Patient dosing will be done at home, except on days of study visits.

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 patients in Group 1 and Group 2 and additionally at Weeks 14 and 16 for patients in Group 2 who dose-escalate to 400 mg daily. Patients from Group 1 rolling over into Group 2 will continue the visit schedule for Group 2 without dose interruption; for these patients, Week 12 will be their baseline visit for Group 2 and they will not undergo the Group 1 4-week follow-up visit. The following safety measurements will be performed during each in-clinic visit: AE reporting, safety laboratories, physical exams, vital signs, ECGs, concomitant medications and pregnancy tests. Key efficacy parameters will also be measured including effects on: glucose tolerance, blood pressure, cortisol concentration, body/weight composition and metabolism. Predose and postdose samples for serial PK will be collected at Weeks 2, 6, and 10, and predose trough PK samples only will be collected at Weeks 4, 8, and 12/early termination (ET) for patients in Group 1. 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.

Figure 2 CORT125134-451 Study Design



3.2 Data Review Committee

An independent DRC consisting of at least one physician experienced in the evaluation and treatment of patients with Cushing's syndrome, a clinical pharmacologist, and a statistician will review CORT125134 PK and safety data. Data will be reviewed in accordance with procedures detailed in a separate DRC Charter. The DRC meeting timelines and role are described below:

The DRC will convene:

- For oversight of Group 1:
  - When 6 evaluable patients have escalated to Dose 3 of Group 1 (200 mg), and steady-state PK and safety data are available (to confirm the appropriateness of the Group 1 dose levels)
  - When 12 evaluable patients have escalated to Dose 3 of Group 1, and steady-state PK and safety data are available
- For oversight of Group 2:
  - When 6 evaluable patients have escalated to Dose 3 or 4 (whichever is the patient's highest Group 2 dose) and PK and safety data are available
  - At end of study

- Overall, no less than every 6 months while the study is in progress

The DRC will perform the following tasks:

- Evaluate PK data from the study in concert with the results of updated PK modeling [redacted]
- Recommend changes, if applicable, to any planned dose levels [redacted]

The DRC's evaluation of PK results for groups of patients and their review of the PK simulations and estimated exposures based on PK modeling will complement the Medical Monitor's review of individual dose escalations.

In the event that a decision is made by the Sponsor to reject a safety recommendation by the DRC, the decision and rationale will be communicated to the Food and Drug Administration (FDA) and site IRBs before enrolling additional patients.

4 STUDY POPULATION

The following eligibility criteria are designed to select patients for whom protocol treatment is considered appropriate. All relevant medical and nonmedical conditions will be taken into consideration when deciding whether this protocol is suitable for a particular patient.

Approximately 30 patients with a confirmed diagnosis of endogenous Cushing's syndrome and at least one of the following will be enrolled in this study:

- Type 2 diabetes or impaired glucose tolerance (at least 6 patients in both Group 1 and Group 2).
- Uncontrolled or untreated hypertension (at least 6 patients in both Group 1 and Grou 2).

Possible etiologies of Cushing's syndrome include Cushing's disease, ectopic ACTH-secreting tumors, ectopic corticotropin releasing hormone-secreting tumors, adrenal cortisol-secreting adenomas, adrenocortical carcinoma, primary pigmented nodular adrenal disease (PPNAD), or primary macronodular adrenal hyperplasia (PMAH).

4.1 Inclusion Criteria

Patients must meet the following criteria in order to participate in the study:

1. Is a male or female adult, 18–80 years of age
2. Has a diagnosis of endogenous Cushing's syndrome confirmed by:
   At least two of the following test criteria (Nieman 2008):
   - Urinary free cortisol above the upper limit of normal (50.0 µg/24 h) in at least 2, and up to 4, complete 24-hour collections within 3 weeks prior to Day 1 (baseline)
   - Late-night salivary cortisol above the upper limit of normal (at least 2, and up to 4, collections using a salivette) within 3 weeks prior to Day 1 (baseline)
   - Lack of cortisol suppression (>1.8 µg/dL serum cortisol) on either 1-mg overnight or 2-mg 48-hour dexamethasone suppression testing (DST) during screening or within 12 weeks before the ICF is signed.

And

At least two of the following clinical signs and symptoms of Cushing's syndrome:

- Facial characteristics of a Cushingoid appearance (moon facies, dorsocervical fat pad, plethora)
- Increased body weight or central obesity
- Proximal muscle weakness
- Low bone mass (dual energy X-ray absorptiometry [DXA] T < −1.0)
- Psychiatric symptoms (including depression or psychosis)
- Hirsutism and/or violaceous striae and/or acne
- Easy bruising

A patient with an adrenal lesion may alternatively qualify if there is autonomous cortisol secretion based on dexamethasone suppression testing (Fassnacht 2016) and supporting evidence of clinically significant cortisol excess. Such a patient must have:

- Radiologically proven unilateral or bilateral adrenal disease (nodules, hyperplasia)

- Lack of cortisol suppression (>5 µg/dL serum cortisol) on either 1-mg overnight or 2-mg 48-hour dexamethasone suppression testing during screening
- Low or suppressed ACTH (<10 pg/mL) to confirm ACTH-independency
- Presence of at least two comorbidities potentially related to cortisol excess (e.g. type 2 diabetes, hypertension, obesity, osteoporosis), of which at least one is inadequately controlled by medical measures

3. Requires medical treatment of hypercortisolemia (ie, those for whom surgery or radiation is contraindicated or has been refused)

   Examples include, but are not limited to, patients with Cushing's disease who are post-surgery and/or post-radiation for whom additional surgery is not recommended; de novo patients with Cushing's disease who are not eligible for surgery due to comorbidities; and patients with ectopic ACTH-dependent Cushing's syndrome in which the tumor cannot be localized or completely removed.

4. Meets at least one of the following criteria:
   - Has type 2 diabetes mellitus as confirmed at screening visit with a fasting glucose >126 mg/dL and 2-hour oral glucose tolerance test (oGTT) result for plasma glucose ≥200 mg/dL at 2 hours (Standards of Medical Care in Diabetes – 2015)
   - Has impaired glucose tolerance (2-hour oGTT result for plasma glucose in the range of ≥140 mg/dL to <200 mg/dL) (Standards of Medical Care in Diabetes – 2015)
   - Has hypertension (mean systolic BP of 130–170 mmHg and/or a mean diastolic BP of 85–110 mmHg) based on 24-hour ambulatory BP measurements (O'Brien 2013)
5. If taking antidiabetic medication, is on a stable dose (ie, cannot start new medication or change dose within 4 weeks prior to the first dose of study drug)
6. If taking antihypertensive medication, is on a stable dose (ie, cannot start new medication or change dose within 4 weeks prior to the screening ambulatory BP measurement)
7. Has potassium within the normal range (3.5 to 5.3 mEq/L) at screening or corrected to within the normal range by Day 1
8. Female patients of childbearing potential must be willing to use a highly effective method of contraception from 30 days prior to Day 1 until 30 days after the last dose of study drug. Male patients with a female partner must agree to 2 forms of contraception, one of which must be a double-barrier method, from Day 1 until 30 days after the last dose of study drug. Highly effective methods of contraception include abstinence, oral contraceptives plus barrier method, diaphragm with vaginal spermicide, intrauterine device, condom and partner using vaginal spermicide, and surgical sterilization (≥6 months post-surgery).
9. (Female patients): Has a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline (Day 1)
10. Has a life expectancy of at least 6 months
11. Is able to participate in the study for up to 22 weeks in Group 1 and 26 weeks in Group 2, including returning to the investigative site to fulfill the safety and efficacy evaluations outlined in the protocol
12. Is able to read and understand the consent form and communicate with the study staff

13. Provides written consent to participate in the study prior to any study procedures and understands that he/she is free to withdraw from the study at any time

4.2 Exclusion Criteria

Patients who meet any of the following exclusion criteria will not be eligible to participate in the study:

1. Has a non-endogenous source of hypercortisolemia
2. Has pseudo-Cushing's syndrome. Patients with known or suspected pseudo-Cushing's syndrome based on medical history (such as patients with severe obesity, major depression, or a history of alcoholism) should undergo a dexamethasone-CRH/DDAVP stimulation test (Yanovski 1993, Giraldi 2007, Yanovski 1998) to rule-in or rule-out this possibility.
3. Has uncontrolled, clinically significant hypothyroidism or hyperthyroidism
4. Has poorly controlled hypertension, defined as systolic BP >170 mmHg or diastolic BP >110 mmHg at screening
5. Has Stage ≥4 renal failure (ie, glomerular filtration rate ≤29 mL/min)
6. Has elevated total bilirubin >1.5×ULN or elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3×ULN
7. For patients with diabetes or abnormal oGTT at screening: has glycated hemoglobin (HbA1c) of >12% within 3 months of first dose of study drug
8. Has a screening hemoglobin level of <9 g/dL
9. Has a clinically significant electrocardiogram (ECG) abnormality at screening, which, in the opinion of the Investigator, will make the patient an unsuitable candidate for the study
10. Has a confirmed screening QTcF interval >450 ms for males and >470 ms for females (using Fridericia's correction) in the presence of a normal QRS interval (QRS <120 ms) or a history of additional risk factors for torsades de pointes
11. Is currently receiving chemotherapy for a tumor related to Cushing's syndrome
12. Had radiation therapy for Cushing's syndrome-related tumor within 1 year of screening period
13. Is planning surgery or radiation therapy for Cushing's syndrome-related tumor during the study
14. Has used or plans to use of any of the following treatments for Cushing's syndrome, as specified:
    - Adrenostatic medications: metyrapone, ketoconazole, fluconazole, aminoglutethimide, or etomidate from 4 weeks prior to baseline (Day 1) through the follow-up visit
    - Adrenolytic medications:
      – In Group 1, any patients taking mitotane
      – In Group 2 only, patients with adrenocortical carcinomas taking mitotane whose dose has not been stable for at least 2 months prior to baseline (Day 1) or in whom increases in the mitotane dosage are expected through the end of dosing.
    - Neuromodulator drugs that act at the hypothalamic-pituitary level: serotonin antagonists (cyproheptadine, ketanserin, ritanserin), dopamine agonists (bromocriptine, cabergoline), gamma-aminobutyric acid agonists (sodium valproate), and somatostatin receptor ligands (octreotide long-acting release [LAR], pasireotide

LAR, lanreotide) from 8 weeks before baseline (Day 1) through the follow-up visit. Use of short-acting somatostatin analogs (octreotide, pasireotide) from 4 weeks prior to baseline (Day 1) through the follow-up visit.

- Mifepristone, from 6 weeks before baseline (Day 1) through the follow-up visit.

15. Has started or increased (or plans to start or increase) the dose of an antidepressant medication (eg, selective serotonin reuptake inhibitors or tricyclic compound) from 6 weeks before baseline (Day 1) through the end of the study dosing period
16. Has started or increased (or plans to start or increase) the dose of a lipid-lowering drug from 4 weeks before baseline (Day 1) through the follow-up visit
17. Is lactating
18. Has an acute or unstable medical problem that could be aggravated by treatment with the investigational study drug
19. Has a history of hypersensitivity or severe reaction to the study drug, to a similar class of drug, or to the study drug's excipients
20. Has taken any investigational drug within 30 days before baseline (Day 1), or within a period of less than five times the drug's half-life, whichever is longer
21. In the Investigator's opinion, should not participate in the study or may not be capable of following the study schedule
22. Has known human immunodeficiency virus (HIV) or hepatitis B or C infection
23. Is a family member of one of the Sponsor's employees, the Investigator or the site staff directly working on the study.

4.3 Screening Failures and Rescreening

Patients who fail screening due to a laboratory result may be retested within the screening period without prior Corcept approval. Screening UFC tests may be performed up to four times during the screening period. Salivary cortisol tests may also be performed up to four times during the screening period. The average of the results for each test will serve as the "baseline" for each test. Other laboratory tests during the screening period may be repeated at the Investigator's discretion. The 24-hour ambulatory BP monitoring may be repeated if there is a technical problem with the test.

Whenever patients are rescreened, they must sign an informed consent form each time and be assigned a new patient identification number. The only screening assessments that do not need to be repeated during rescreening are the oGTT and the dexamethasone suppression test.

In patients with an abnormal QTc interval at screening in which no concomitant drugs known to prolong QTc and no electrolyte abnormalities are present, two repeat ECG recordings should be done. The final decision on excluding a patient should be based on the average QTcF interval across the 3 recordings. If an electrolyte abnormality is present, it should be corrected before the ECG is repeated. If the patient is on a concomitant medication known to cause QT prolongation, an alternative medication may be considered and the ECG repeated after an appropriate washout time.

4.4 Patient Withdrawal

Patients may withdraw their consent to participate in the study at any time for any reason without prejudice. The Investigator also has the right to withdraw patients from the study for the following reasons:

- The patient withdraws consent. The Investigator should make a reasonable attempt to document the specific reason why consent is withdrawn.
- The Investigator decides it is in the patient's best interest to discontinue treatment and/or participation in the study. Reasons may include the following:
- Patient requires or starts prohibited medication(s).
- Patient is not adherent to protocol procedures.
- The patient experiences an AE that requires withdrawal from the study.
- Patient is pregnant.
- Patient is lost to follow-up. Before a patient is determined to be lost to follow-up, reasonable efforts will be made to contact the patient and complete study termination procedures.
- The Sponsor terminates the study.

When a patient withdraws, every effort should be made to complete the follow-up examinations.

5 STUDY TREATMENT

5.1 Product Description

5.1.1 Study Drug

CORT125134 is a synthetically prepared small molecule with the following chemical name: (R)-(1-(4-fluorophenyl)-6-((1-methyl-1*H*-pyrazol-4-yl)sulfonyl)-1,4,5,6,7,8-hexahydro-4a*H*-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 7 capsules per strip.

5.1.2 Reference Therapy

No reference therapy will be used in this study.

5.1.3 Placebo

No placebo treatment will be used in this study.

5.2 Treatment Groups

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.

After 6 patients have received CORT125134 through Week 10 (ie, 2 weeks following dose escalation to 200 mg/day), the Data Review Committee (DRC) will review pharmacokinetic (PK) and safety data to confirm appropriateness of dose levels in Group 1.

After 10-week PK data are available from 12 patients in Group 1, the DRC will meet and evaluate PK and safety data

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.

5.3 Blinding

In this open-label study, all study patients, Investigators, the Medical Monitor, Sponsor staff members, and other applicable personnel will be unblinded to study treatment.

5.4 Treatment Administration

5.4.1 Dosing Groups and Dose Escalation

Patients in Group 1 will receive CORT125134 100 mg/day for the first 4 weeks of treatment, then CORT125134 150 mg/day for the second 4 weeks of treatment, and then CORT125134 200 mg/day for the third 4 weeks of treatment. After 6 patients have received CORT125134 through Week 10 (ie, 2 weeks following dose escalation to 200 mg/day), the DRC will review PK and safety data to confirm the appropriateness of dose levels in Group 1. After 12 patients

have completed Week 10 (ie, 2 weeks following dose escalation in Group 1) in the study, the DRC will review PK and safety data and recommend changes, if applicable, to the dose escalation in Group 2. Patients who complete Group 1 may, at the Investigator's recommendation, enter Group 2 and follow the Group 2 dose escalation schedule.

Patients in Group 2 will receive CORT125134 250 mg/day for the first 4 weeks of treatment. Thereafter, the dose escalates to CORT125134 300 mg/day for the second 4 weeks of treatment, to CORT125134 350 mg/day for the third 4 weeks of treatment, and then to CORT125134 400 mg/day for the fourth 4 weeks of treatment. 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 dose escalations must be approved by the Medical Monitor.

Group	First 4 Weeks of Treatment	Second 4 Weeks of Treatment	Third 4 Weeks of Treatment	Fourth 4 Weeks of Treatment
1	100 mg (50-mg capsule × 2)	150 mg (50-mg capsule × 3)	200 mg (50-mg capsule × 4)	Not applicable
2	250 mg (50-mg capsule × 5)	300 mg (50-mg capsule × 6)	350 mg (50-mg capsule × 7)	400 mg (50-mg capsule × 8)

The assigned dose will be administered orally once daily in the morning, with no food for 4 hours before and 1 hour after dosing. Any other medication(s) that the patient is taking should be taken 30 minutes after the dose of study drug.

Patients will be instructed to take the appropriate number of 50-mg capsules to equal the prescribed daily dose (eg, 3 capsules for the 150-mg dose, 5 capsules for the 250-mg dose).

5.4.2 Per-Protocol Dose Escalation

After completing Weeks 4 and 8 of treatment, patients will escalate their doses [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.4.3 Dose Reductions

Dose reductions may be performed according to the following rules:

- The Investigator may reduce the dose of CORT125134 for AEs or tolerability issues to the next lower dose (eg, from 200 to 150 mg/day or from 350 to 300 mg/day).
- With the approval of the Medical Monitor, the Investigator may subsequently increase the dose to the previous dose (eg, from 150 back to 200 mg/day or from 300 back to 350 mg/day).
- If the dose of CORT125134 is reduced, a subsequent dose increase should be avoided within 7 days of a Week 2, Week 6, or Week 10 PK evaluation.
- Further dose escalations at Week 4 or Week 8 (as with all escalations) must be approved by the Medical Monitor.
- Patients enrolled in Group 2 who cannot tolerate the starting dose selected for Group 2 (ie, planned to be 250 mg) will be allowed to continue on-study at the next lower dose level (ie, 200 mg). Subsequent dose increases/escalations will follow the rules listed above.

Dose reductions based on excessive GR blockade are outlined in Section 7.14.4.1.

5.4.4 Missed Doses

Patients will be advised to take a missed dose on the same day of the missed dose, but not the following day; that is, no more than one dose on any day. Missed doses should be taken on an empty stomach, at least 4 hours after a meal, and no food should be consumed for 1 hour after the dose. The patient should inform the Investigator when a dose is not taken. Missed doses will be documented in the source documents.

5.4.5 Study Drug Interruptions

Study drug can be interrupted and restarted if the Investigator or Medical Monitor thinks that it is warranted in a particular patient. During study drug interruptions, patients will continue on the same visit schedule.

Study drug interruptions due to excessive GR blockade are detailed in Section 7.14.4.1.

5.5 Treatment Compliance

Patients will be provided with a diary card to record doses taken at home and will be instructed to bring used and unused packages of study drug to each study visit. Study staff will count and record the number of capsules taken and returned at each study visit to determine patient compliance. At each visit, the patients will be instructed on proper study drug administration. Adherence to the study protocol will be reinforced at each visit and during the weekly contact (telephone or email).

Study staff will document dosing information on the source document. They will also count and record the number of capsules taken and returned at each study visit.

5.6 Manufacturing, Packaging, and Labeling

The study drug will be manufactured and packaged under Good Manufacturing Practice (GMP) regulations. The capsules are provided in sealed, foil blister packs.

At a minimum, the label on each package of study drug will contain the drug name, protocol number, storage conditions, statement on investigational use only, and Sponsor details. Labeling will meet country-specific requirements.

5.7 Storage and Accountability

The investigational product CORT125134 should be stored at 25°C (77°F); excursions are permitted from 2–30°C (36–86°F).

The Investigator is responsible for the accountability of all used and unused study medication. All investigational materials should be kept in a secure area inaccessible to unauthorized individuals.

Drug accountability records must be maintained at the site and be available for monitoring by the Sponsor or its representatives. At a minimum, records will be maintained to document receipt of supplies, dispensing of supplies to specific patients, and return of unused product by patients.

Opened and unopened packages of study drug must be returned to the Sponsor or its designee at the end of the study or destroyed onsite, after study drug accountability monitoring has occurred, in accordance with local requirements.

Under no circumstances will the Investigator allow the investigational drug to be used other than as directed by the protocol.

6 PRIOR AND CONCOMITANT MEDICATIONS

6.1 Prohibited Medications/Treatments

The following prior/concomitant medications are not allowed:

- Medications used in the treatment of Cushing's syndrome are prohibited and require washout (as applicable) during screening provided the intervals specified in Exclusion Criterion 14 fit within the screening window.
  - Adrenostatic medications: metyrapone, ketoconazole, fluconazole, aminoglutethimide, or etomidate
  - Neuromodulator drugs that act at the hypothalamic-pituitary level: serotonin antagonists (cyproheptadine, ketanserin, ritanserin), dopamine agonists (bromocriptine, cabergoline), gamma-aminobutyric acid agonists (sodium valproate), and somatostatin receptor ligands (octreotide long-acting release [LAR], pasireotide LAR, lanreotide) from 8 weeks before baseline (Day 1) through the follow-up visit. Use of short-acting somatostatin analogs (octreotide, pasireotide) from 4 weeks prior to baseline (Day 1) through the follow-up visit.
  - Mifepristone, from 6 weeks before baseline (Day 1) through the follow-up visit.
- Group 1 only: Mitotane
- Start of a new antidepressant medication (see Exclusion Criterion 15)
- Strong CYP3A4 inhibitors (including grapefruit, grapefruit juice, or grapefruit-containing products)
- Start of a new lipid-lowering drug (see Exclusion Criterion 16)
- Other investigational agents
- Corticosteroids:
  - Systemic corticosteroids
  - Potent (Group III) topical corticosteroids
  - Potent intra-articular corticosteroids

6.2 Potential Drug-Drug Interactions

CORT125134 has been shown to inhibit the activity of CYP3A4 and CYP2C8 and may inhibit CYP3A5, CYP2C9, CYP2C19, and CYP2D6. Drugs metabolized by these isozymes, particularly drugs with a narrow therapeutic ratio, should be used with caution within 1 week prior to baseline (Day 1) through the follow-up visit, unless otherwise indicated.

6.3 Rules for Concomitant Medications

- If hypokalemia ensues during therapy with CORT125134, patients may be given mineralocorticoid receptor antagonists, other potassium-sparing diuretics, and potassium supplements (see Section 7.14.4.2).
- Patients in Group 2 receiving mitotane should not increase the mitotane dosage through the end of dosing (see Exclusion Criterion 14). Decreases in dose are allowed.

- The oGTT should be done fasting. In general, the patient should not take the antidiabetic oral medication in the morning of their visit. To avoid hypoglycemia, insulin cannot be taken prior to the oGTT. Long-acting insulin can be taken the night before the oGTT. Oral antidiabetes medications and insulin preparations can be taken with food after the completion of the oGTT
- Insulin and other medications for diabetes can be decreased during the dosing period to prevent hypoglycemia, but upward titration should be avoided and occur only after consultation with the Medical Monitor.
- Antihypertensive medication can be decreased during the dosing period to prevent hypotension or orthostatic symptoms. Increase of the dose of antihypertensive medication or addition of new antihypertensive medication should be avoided and occur only after consultation with the Medical Monitor.
- An increase in dose of a current lipid-lowering drug is not allowed from 4 weeks before baseline (Day 1) through the follow-up visit (see Exclusion Criterion 16).
- An increase in dose of a current antidepressant medication is not allowed from 6 weeks before baseline (Day 1) through the end of the study dosing period (see Exclusion Criterion 15).

7 STUDY ASSESSMENTS

7.1 Informed Consent

Prior to performing any study-related procedures, the patient must sign and date an Institutional Review Board (IRB)-approved informed consent form (ICF). (See Section 11.3 for additional information about informed consent.) Health Insurance Portability and Accountability Act authorization, if applicable, will also be obtained. The informed consent process must be thoroughly documented in the patient's record. Patients can be screened up to 42 days prior to the first dose of study drug on Day 1.

7.2 Medication Washout

Medications used in the treatment of Cushing's syndrome are prohibited and require washout (as applicable) during screening provided the intervals specified in Exclusion Criterion 14 fit within the screening window. Patients requiring washout of a medication for Cushing's 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.

7.3 Demographics and Baseline Disease 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's syndrome type (eg, EAS, PPNAD, PMAH), will also be documented.

7.4 Medical History and Medication History

Patient medical history will be obtained at screening, including the diagnosis, etiology, and treatment history of Cushing's 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.

7.5 Pituitary Magnetic Resonance Imaging (MRI) Scans

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 as standard of care will be collected if available.

7.6 Dexamethasone Suppression Test (DST)

The dexamethasone suppression test (DST) should be performed at screening when an additional test is required to confirm endogenous Cushing's syndrome (eg, if either the 24-hour UFC or late night salivary test results are within normal range and an additional test is required to confirm Cushing's syndrome).

In patients with adrenal incidentalomas, if the biochemical confirmation of cortisol excess cannot be made by late night salivary test and UFC, a 1-mg overnight or 2-mg 48-hour dexamethasone suppression test (DST) can be done.

7.7 Study Enrollment

Patients who meet all of the inclusion criteria and none of the exclusion criteria during the screening period and at baseline (Day 1) will be enrolled in the study. Refer to Section 5.2 for the method of assigning patients to dose groups.

A screening log will be maintained and will include all patients who sign the ICF whether or not they are enrolled. Reasons for screen failure will be recorded.

7.8 Study Treatment Dispensing

Study drug will be dispensed to each patient at baseline (Day 1) and, at a minimum, at Weeks 2, 6, 8, and 10 for Group 1 and at Weeks 2, 6, 8, 12, and 14 for Group 2. Sufficient study drug will be provided for the period between visits.

7.9 Drug Compliance Assessment

Patients will be instructed to bring used and unused packages of study drug to each study visit. At each visit, patients will be instructed on proper study drug administration. Adherence to the study protocol will be reinforced at each visit and during the weekly contact (telephone or email).

At each visit starting with Day 1, study staff will document dosing information in the source document. They will also count and record the number of capsules taken and returned at each study visit.

7.10 Patient Diary

Patient diary is dispensed to the patient at baseline and at Weeks 2, 4, 6, 8, and 10 for Group 1 and at Weeks 2, 4, 6, 8, 10, 12, and 14 for Group 2. Diaries should be completed by the patient on a daily basis to capture whether study drug was taken per protocol. Diary cards should be returned and reviewed at Weeks 2, 4, 6, 8, 10, and 12 for Group 1 and at Weeks 2, 4, 6, 8, 10, 12, 14, and 16 for Group 2.

7.11 Efficacy Assessments

7.11.1 Key Efficacy Assessment

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

7.11.1.1 Effects on Glucose Tolerance

A 2-hour 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/early termination (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. In general, the patient should not take the antidiabetic oral medication in the morning of their visit. To avoid hypoglycemia, insulin cannot be taken prior to the oGTT. Long-acting insulin can be taken the night before the oGTT. Oral antidiabetes medications and insulin preparations can be taken with food after the completion of the oGTT.

7.11.1.2 Effects on Blood Pressure

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.) 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. The patient should use the monitor during a time when a full 24-hour recording can be made.

An ambulatory BP monitor will be given to the patient at screening, and the patient will bring the monitor to each study visit or will send it to the study site in advance of the next study visit.

7.11.2 Exploratory Efficacy Assessments

7.11.2.1 Physician's Global Assessment

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

7.11.2.2 Effects on Glucose Tolerance

7.11.2.2.1 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 screening, baseline (Day 1), and Week 12/ET for Group 1 and at screening, baseline, and Weeks 12 and 16/ET for Group 2.

7.11.2.2.2 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.

7.11.2.2.3 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.

7.11.2.3 Effects on Cortisol Concentration

The following tests will be performed in all patients in order to assess eligibility for the study and also to assess the changes in cortisol levels during the study period.

7.11.2.3.1 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 7 days prior to the visits on Weeks 2, 4, 6, 8, 10, and 12/ET for Group 1 and also within 7 days prior to the visits on Weeks 2, 4, 6, 8, 10, 12, 14, and 16/ET visits for Group 2.

Each patient will be provided with instructions and supplies to collect all the urine produced during a 24-hour period. The 24-hour urine creatinine level and the total 24-hour urine volume will be obtained to confirm complete collection of the urine. The patient should avoid drinking an unusual amount of fluids (≥5 L/day) during the 24-hour period. Patients should avoid use of any glucocorticoid preparations, including -steroid-containing skin or hemorrhoid creams, during the collection period.

See Section 7.11.2.15 for urine calcium and sodium measurements from same samples.

Complete instructions for the patient will be provided.

7.11.2.3.2 Late-Night Salivary Cortisol Test

This test will be performed at least two times during each of the following: screening period and within 7 days prior to the visits on Weeks 2, 4, 6, 8, 10, and 12/ET for Group 1 and also within 7 days prior to the visits on Weeks 2, 4, 6, 8, 10, 12, 14 and 16/ET for Group 2.

The patient will be given supplies for the collection of saliva at home prior to a clinic visit. Samples should be collected at bedtime.

Complete instructions for the patient will be provided.

7.11.2.4 Effects on Body Weight and Composition

The following assessments will be performed on all enrolled patients.

7.11.2.4.1 Body Weight Measurement

Body weight will be obtained at every visit.

7.11.2.4.2 Waist Circumference Measurement

Waist circumference will be measured at baseline (Day 1); at Weeks 4, 8, and 12/ET for Group 1 and at Weeks 4, 8, 12, and 16/ET for Group 2; and at the follow-up visit. Clinical sites will be provided with tape measures to ensure consistency.

7.11.2.5 Central Nervous System/Psychiatric and Quality-of-Life Effects

The following assessments will be performed on all enrolled patients.

7.11.2.5.1 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. Total scores are classified as minimal, mild, moderate, and severe depression, with larger scores indicating more severe depressive symptoms. Patients will complete the BDI-II 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.

7.11.2.5.2 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 will be administered 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.

7.11.2.5.3 CushingQoL

The CushingQoL patient questionnaire evaluates the health-related quality of life in patients with Cushing's syndrome (Webb 2008). It comprises 12 questions, each with 5 possible answers. The CushingQoL instrument addresses known problem areas associated with Cushing's 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 will be administered at baseline (Day 1), at Weeks 4, 8, and 12/ET for Group 1 and at Weeks 4, 8, 12, and 16/ET for Group 2, and at the follow-up visit.

7.11.2.6 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, and 12/ET for Group 1 and Weeks 4, 8, 12, and 16/ET for Group 2, and at the follow-up visit for a lipid panel analysis.

7.11.2.7 Effects on Strength

The sit-to-stand test will be performed by all enrolled patients.

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

Patients seated in a chair will be asked to fold their arms across their chests and to stand up from the seated position once; if they are able to successfully rise from the chair, they will be asked to

sit down again and then stand up and sit down five times as quickly as possible. The chair should be of standard height so that the patient's legs are in flexion of approximately 90 degrees about the knee when the feet are flat on the floor. Patients should be advised not to place their feet far beneath chair and not to offset the feet in the horizontal plane (ie, asked to place their feet under the front of the chair, not too far forward (in front of the chair) or too far back (under the chair seat). 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. Patients with gait or balance disorders are not required to complete the sit-to-stand test. The same or similar chair should be used for all measurements.

7.11.2.8 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 baseline and the Week 16/ET visit for Group 2.

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

7.11.2.9 Coagulation Effects

Blood samples will be obtained from all enrolled patients at baseline (Day 1) and at Weeks 4, 8, and 12/ET for coagulation tests for Group 1 and at baseline and 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.

7.11.2.10 Glucocorticoid Reception (GR) Activity Biomarkers

A blood sample will be obtained from all patients for analysis of 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. See the laboratory manual for details of preparation, storage, and shipping of these samples.

7.11.2.11 Bone Effects

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

Urine calcium will be measured in the 24-hour UFC test (see Section 7.11.2.3.1).

7.11.2.12 HPA Axis Effects

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

7.11.2.13 ACTH Precursors

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

7.11.2.14 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) and at Weeks 4, 8, and 12/ET for Group 1, and at baseline and Weeks 4, 8, 12, and 16/ET for Group 2.

7.11.2.15 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's 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), and for Group 1 at Weeks 2, 4, 6, 8, 10, and 12/ET and for Group 2 at Weeks 2, 4, 6, 8, 10, 12, 14, and 16/ET.

7.11.2.16 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); at Weeks 4, 8, and 12/ET for Group 1; and at Weeks 4, 8, 12, and 16/ET for Group 2.

7.11.2.17 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), and at Weeks 2, 4, 6, 8, 10, and 12/ET for Group 1. For Group 2, samples will be collected at screening, baseline, and at Weeks 2, 4, 6, 8, 10, 12, 14, and 16/ET visits.

7.12 Pharmacokinetic Assessments

For Group 1, 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. For Group 2, 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.

The time windows for collection of PK samples are listed below:

Nominal Time	Reporting Standards
Predose	Up to 60 minutes before dosing
1 hour postdose	±5 minutes
2 hours postdose	±10 minutes
4, 6, and 8 hours postdose	±15 minutes

Dose escalations will proceed according to the procedures outlined in Section 5.4.2. For patients in Groups 1 and 2, the first planned escalation of dose will take place the day after the Week 4 visit, and the second planned escalation of dose will take place the day after the Week 8 visit. For patients in Group 2, the third planned escalation of dose will take place the day after the Week 12 visit.

In case of a recent or pending dose interruption or dose reduction, the PK sampling day at Weeks 2, 6, 10, or 14 may be adjusted (ie, made earlier or later) to try to capture at least 7 days of administration of the current dose of study drug before PK sampling. (Otherwise, all testing windows in the Schedule of Events [Sections 13.1 and 13.2] must be followed.)

If a scheduled dose escalation is cancelled, the patient will provide subsequent blood samples for all trough CORT125134 levels only (ie, full PK profiles at Weeks 6, 10, or 14 will not be performed).

If, as a result of a dose reduction, a Weeks 6, 10, or 14 full PK profile would be redundant (ie, a full PK profile was already successfully obtained at the patient's current dose), it will not be repeated.

7.13 Safety Assessments

7.13.1 Physical Examination

A complete physical examination will be conducted at screening and baseline (Day 1); 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; and at the follow-up visit. 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.

Height will be measured at the screening visit only.

7.13.2 Vital Sign Measurements

Vital signs include BP, heart rate, respiratory rate, and oral body temperature. Blood pressure and heart rates will be obtained in the dominant arm (writing arm), if possible, with the patient in a sitting position after resting for approximately 5 minutes. Automated BP machines can be used to standardize measurements. Vital signs will be collected in the clinic at screening and baseline (Day 1); 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; and at the follow-up visit. In addition, unscheduled assessments of vital signs can be performed as necessary.

In addition to the safety vital signs collected, a 24-hour ambulatory BP test will also be done by all patients at screening and by patients in the hypertension subgroup at post-screening time points to assess the effect of CORT125134 on BP (see Section 7.11.1.2).

7.13.3 Electrocardiogram

Twelve-lead ECG tracings will be obtained in triplicate from all patients at screening and in duplicate 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, and the follow-up visit. Patients should be lying down for at least 10 minutes prior to each ECG evaluation. A central reviewer will be used; instruction will be provided in the study manual.

At Weeks 2, 4, 6, 8, 10, 12, 14, and ET, the ECG 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.

7.13.4 Pregnancy Tests and Contraception Methods

All female patients of childbearing potential (including all women <50 years old, women whose surgical sterilization was performed <6 months ago, and women who have had a menstrual period in the last 2 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.

Female patients of child bearing potential are required to use a highly effective method of contraception from 30 days prior to Day 1 to 30 days following the last dose of study drug administration. Male patients with female partners are required to use to use 2 forms of contraception, one of which is a double-barrier method, from Day 1 (prior to study drug administration) until 30 days following the last dose of study drug administration.

Highly effective forms of contraception include:

- Abstinence
- Surgical sterilization
- Intrauterine device or intrauterine system
- Oral contraception plus a barrier method
- Double-barrier method (eg, male condom or a diaphragm plus a vaginal spermicidal cream)

If a patient is usually not sexually active but becomes active, they, with their partner, must comply with the contraceptive requirements detailed above. In addition, males should not donate sperm until 30 days after the last dose of study drug.

7.13.5 Safety Clinical Laboratory Tests

Complete instructions for sample processing and shipment will be provided in the Central Laboratory Manual.

7.13.5.1 Laboratory Parameters

Fasting blood samples will be collected for the analysis of safety in all patients at screening, baseline (Day 1); 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; and the follow-up visit. 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. An abnormal laboratory value that leads to a dose modification or patient withdrawal from the study will be recorded as an AE on the eCRF. Other clinically significant laboratory values may be reported as AEs at the discretion of the Investigator. Patients with a clinically significant out-of-range laboratory value will be followed until the laboratory value returns to normal, or becomes medically stable. The Investigator will treat the patient as medically required at appropriate intervals until this occurs.

The Investigator will review all laboratory reports, evaluate the results, and sign/date the report.

Safety laboratory measurements will include the following:

Chemistry:

- 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:

- 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, red blood cell (RBC) count, and WBC count
- Differential: percent and absolute for the following: basophils, eosinophils, lymphocytes, monocytes, and neutrophils

7.13.5.2 Sample Collection, Storage, and Shipping

Complete instructions for collection, preparation, and shipping of all laboratory samples will be provided by the central laboratory/ies in a laboratory manual. Shipping instructions for samples collected for PK analysis, ACTH precursors, and GR activity biomarkers will also be provided.

The total volume of blood to be collected from each patient will be no more than 731 mL for Group 1 and 908 mL for Group 2 during the 12-week and 16-week treatment periods, respectively.

7.13.6 Safety Event Documentation and Reporting

7.13.6.1 Investigator's Responsibilities

Investigators are responsible for monitoring the safety of patients who have entered this study and for providing appropriate medical care. Investigators are required to report promptly to

Corcept Therapeutics or its designee any AE that may reasonably be regarded as caused by, or probably caused by, the study drug. If the adverse effect is alarming, the Investigator should report the adverse effect immediately. In addition, the Investigators are responsible for alerting Corcept Therapeutics or its designee to any event that seems unusual, even if the event may be considered an unanticipated benefit to the patient, and for reporting the event on the appropriate eCRF or safety report form.

By exercising appropriate healthcare options, the Investigator remains responsible for managing AEs that are serious or that cause a patient to withdraw before completing the study. Frequency of follow-up of any particular AE is left to the discretion of the Investigator. Duration of follow-up and requirements for *immediate* SAE reporting (within 24 hours of the event) are described below.

7.13.6.2 Monitoring Safety Data During Study

Safety results collected during the study (eg, AEs, laboratory test results, physical findings) will be monitored on an ongoing basis by the Medical Monitor and Investigator.

7.13.6.3 Definition of an Adverse Event

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. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product that emerges or worsens relative to the patient's pretreatment baseline, whether or not it is considered to be related to the investigational product.

Illnesses present before the patient signs the informed consent form (ICF) are considered pre-existing conditions and are documented on the medical history eCRF. Pre-existing conditions that worsen during the study are entered on the AE eCRF.

7.13.6.4 Definition of a Serious Adverse Event

An SAE is any AE that meets any of the following criteria:

- Results in death (ie, the AE caused or led to the fatality).
- Is life-threatening (ie, the AE refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires hospitalization or prolongation of existing hospitalization (ie, hospitalizations for scheduled treatments and elective medical/surgical procedures are not SAEs by this criterion).
- Results in persistent or significant disability/incapacity (ie, the AE results in substantial reduction of the patient's ability to perform activities of daily living).
- Results in a congenital anomaly or birth defect (ie., an adverse finding in a child or fetus of a patient exposed to the study medication before conception or during pregnancy);
- Involves other medically important conditions (ie, the AE does not meet any of the above serious criteria but based on appropriate medical judgment, may jeopardize the patient or

require medical or surgical intervention to prevent one of the serious outcomes listed in these criteria).

7.13.6.5 Clinical Laboratory Adverse Events

All out-of-range laboratory values will be determined to be clinically significant or not clinically significant by the Investigator. An abnormal laboratory value that leads to a dose modification or patient withdrawal from the study will be recorded as an AE on the eCRF. Other clinically significant laboratory values may be reported as AEs at the discretion of the Investigator.

7.13.6.6 Documentation of Adverse Events

Patients will be evaluated and questioned to identify AEs during the study.

Collection of AEs will start immediately following signing of the ICF and will continue throughout the study. Illnesses present before the patient signs the informed consent form (ICF) are considered pre-existing conditions and are documented on the medical history eCRF. Pre-existing conditions that worsen during the study are entered on the AE eCRF. Adverse events that occur after start of study treatment and up to and including 28 days after administration of the last dose of study drug will be considered TEAEs. Any AEs reported more than 28 days after the last dose of study drug will be considered posttreatment AEs.

All AEs will be documented on the AE eCRF and in the patient's medical record. The following attributes must be assigned: (1) description, (2) dates of onset and resolution, (3) severity (see Section 7.13.6.7.1), (4) relationship to the study medication (see Section 7.13.6.7.2), (5) "serious" criteria if applicable (see Section 7.13.6.4), and (6) action taken. The Investigator will actively solicit this information and assess the AEs in terms of severity and relationship to study drug. The Investigator will treat the patient as medically required until the AE either resolves or becomes medically stable. This treatment may extend beyond the duration of the study. The Investigator will record treatment and medications required for treatment on the appropriate eCRF(s).

In the event that a patient is withdrawn from the study because of an AE, the event must be recorded on the Termination eCRF as the reason for discontinuation.

All AEs considered to be related (see Section 7.13.6.7.2) to study drug and all SAEs will be followed until resolved or until a stable status has been achieved.

All AEs that are drug-related and unexpected (not reported in the Investigator's Brochure or if the event is of greater severity or frequency than that described in the Investigator's Brochure) must be reported to the governing IRB/Independent Ethics Committee (IEC) as required by the IRB/IEC, local regulations, and the governing health authorities.

7.13.6.7 Adverse Event Classification

7.13.6.7.1 Severity Grades of Adverse Events

The seriousness of an AE should not be confused with its severity. To describe the maximum severity of the AE on the AE eCRF, the Investigator will use the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 (CTCAE 2010). For

events not listed in the CTCAE, the definitions from the CTCAE provided in Table 5 should be used to evaluate the grade of severity for the AE.

Table 5 Adverse Event Grades Based on the Common Terminology Criteria for Adverse Events

Grade	Description
1	**Mild**: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	**Moderate**: minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, and managing money)
3	**Severe**: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (eg, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)
4	**Life-threatening**: Life-threatening consequences; urgent intervention indicated
5	**Death**: Death related to AE

Source: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 (CTCAE 2010).

7.13.6.7.2 Relationship of Adverse Event to Study Drug or Procedure

The Investigator responsible for the patient's care (or qualified designee) will assess causality of AEs and SAEs based on the causal attribution guidance in Table 6. The Investigator's assessment of causality must be provided for all AEs (serious and nonserious).

Table 6 Causal Attribution Guidance for Adverse Events

Not related to study drug	An AE that is judged to be clearly due only to extraneous causes such as diseases, environment, and the like. The cause must be noted on the AE eCRF.
Possibly related to study drug	An AE that might be due to the use of the drug. The relationship in time is reasonable; therefore, a causal relationship cannot be excluded. An alternative explanation is inconclusive, eg, concomitant drug (s), concurrent disease (s).
Probably related to study drug	An AE that might be due to the use of the drug. The relationship in time is suggestive. An alternative explanation is less likely, eg, concomitant drug(s) or concurrent disease(s).

7.13.6.8 Procedures for Reporting a Serious Adverse Event

Any SAE occurring during the study period (beginning with informed consent) and for at least 28 days after the last dose of study drug must be reported within 24 hours to the designated safety contact and recorded on the SAE Form. All patients with an SAE must be followed and the outcomes reported. The Investigator must supply the Sponsor and the IRB/IEC with any additional requested information (eg, autopsy reports and terminal medical reports).

SAE Reporting Contact Details:

- US Toll Free Phone: 1-888-723-2445
- US Fax: 1-888-726-8416
- Ex-USA Fax: 00 800-529-34043
- Global Email: Global.SAEInbox@chiltern.com

1. All SAEs occurring from the time of informed consent until 28 days following the last administration of study medication must be reported to Chiltern Pharmacovigilance within 24 hours of the knowledge of the occurrence
2. Complete the SAE reporting form, including whether the event was or was not related to the investigational drug and send to Chiltern Pharmacovigilance. The clinical staff will obtain and maintain all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the patient within the patient files.
3. Promptly inform the governing IRB/IEC of all serious, unexpected, drug-related events that occur at his or her site or per the IRB/IEC regulations. It is the responsibility of each site to submit IND Safety Reports, as applicable, provided to them by the Sponsor to their IRB or IEC as required by the IRB/IEC, local regulations, and the governing health authorities.
4. Fax or email additional follow-up information, if required or available, to Chiltern Pharmacovigilance within 24 hours of receipt. This information should be included on a follow-up SAE Form, placed with the original SAE Form, and kept with the appropriate section of the eCRF and/or study patient file.

An AE, regardless of seriousness, is considered unexpected if not reported in the Investigator's Brochure or if the event is of greater severity or frequency than described in the Investigator's Brochure.

7.13.6.9 Adverse Event Follow-Up

All AEs will be followed until resolution, until deemed stable by the Principal Investigator, or until the patient is deemed by the Principal Investigator to be lost to follow-up.

7.13.6.10 Emergency Sponsor Contact

In a medical emergency (ie, an event that requires immediate attention regarding the treatment of a patient, operation of the clinical study, and/or the use of investigational product), study site personnel will apply appropriate medical intervention according to current standards of care and contact the Medical Monitor:

[redacted]
Corcept Therapeutics Incorporated
149 Commonwealth Drive
Menlo Park, CA 94025
[redacted]

7.14 Pregnancy

All pregnancies with the estimated date of conception occurring during the study treatment or within 30 days of the last dose of study treatment should be reported immediately to the Sponsor or its designee. The patient will be followed to determine the outcome of the pregnancy, and the outcome will be reported.

7.14.1 Maternal Exposure

If a patient becomes pregnant during the study, the study treatment should be discontinued immediately. Pregnancy itself is not regarded as an AE.

If a pregnancy occurs during the study treatment or within 30 days of the last dose of study treatment, the Investigator or designee will inform the appropriate Sponsor representatives immediately but *no later than 24 hours* of when he or she becomes aware of it. The Investigator or designee will ensure that all relevant information is provided to the responsible Clinical Safety Group. All outcomes of pregnancy must be reported by the Investigator within 24 hours after he or she becomes aware of it.

Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed and documented even if the patient has discontinued the study.

7.14.2 Paternal Exposure

Pregnancy of the patient's partner is not considered to be an AE; however, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed and documented, if possible. To capture information about a pregnancy from the partner of a male patient, the Investigator or designee must first obtain the consent of the male patient's partner. A consent form specific to this situation must be used. The outcome of any conception occurring from the date of the first dose of study drug until 30 days after the last dose should be followed and documented.

7.14.3 Prior and Concomitant Medications

At screening, a list of current medications will be obtained, including start date, dosage, and route of administration, along with any medications taken in the 3 months before screening to treat Cushing's syndrome, diabetes, or hypertension.

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.

Information about concomitant medications will be collected from all patients at each visit from screening through the follow-up visit. Any changes in medications since the last visit will be captured and recorded.

7.14.4 Additional Assessments for Special Safety Events

7.14.4.1 Monitoring for Excessive Glucocorticoid Receptor Blockade

Based on the mechanism of action of CORT125134, there is a theoretical risk of excessive GR blockade, which could manifest with findings such as weakness, tiredness, dizziness, hypoglycemia, dehydration, weight loss, nausea, vomiting, diarrhea and muscle aches. Since CORT125134 does not block the mineralocorticoid receptor, it is unlikely that hypotension would be seen in the absence of anti-hypertensive medication.

At each study visit starting with the baseline visit, patients will be evaluated for signs and symptoms of excessive GR blockade, and for patients who experience symptoms, the following actions should be taken:

- CORT125134 treatment should be ***immediately interrupted*** for at least 3 days and standard supportive care, including fluid resuscitation, as indicated, should be administered without delay.
- Supplemental glucocorticoids may be given in high doses to overcome the GR blockade produced by CORT125134. Initially, parenteral dexamethasone 4 to 10 mg should be considered, followed by additional parenteral or oral doses once or twice daily for 1 to 3 days and tapered thereafter, depending on clinical response. In some cases, higher doses of dexamethasone for longer periods of time may be required.
- If the patient has been receiving treatment with a mineralocorticoid receptor antagonist, consideration should be given to discontinuing it or adjusting the dose, particularly in the presence of hypotension.
- Treatment with CORT125134 should be resumed only if the Investigator believes that the potential benefits outweigh the risks and after a discussion with the Medical Monitor. Dosing may be resumed at the lowest tolerable dose previously administered to the patients. For patients in Group 2 on 250 mg/day, the dose may be reduced to 200 mg/day or 150 mg/day, as deemed appropriate by the Investigator. After 2 weeks, the dose may be maintained at the current dose or may be increased by 50 mg with the approval of the Medical Monitor. (Subsequent dose escalations at Week 4 or Week 8 must also be approved by the Medical Monitor.)

Note: In the event of significant trauma, surgery, or medical illness occurring at any time during the study (through 2 weeks after last dose), supplemental glucocorticoids may be needed to offset the GR blockade even in patients not experiencing signs and symptoms of excessive blockade. After resolution of the physiological stress associated with the event, CORT125134 can be reinitiated at the last dose level the patient was receiving prior to interruption of dosing, if the dosing period of the study has not ended.

At study enrollment, all patients will be given a card to carry with them that identifies their potential risk for excessive GR blockade. The card will contain the following information:

- Mention of CORT125134 use (“glucocorticoid receptor antagonist”)
- Potential need for glucocorticoid use in setting of shock, surgery, or serious illness or injury

- Recommended dose of replacement steroids (4–10 mg dexamethasone intramuscularly or intravenously)
- Investigator contact information

7.14.4.2 Monitoring for Hypokalemia

If a patient develops hypokalemia during the study, oral replacement of potassium (40-120 mEq per day) should be considered. Mineralocorticoid receptor antagonists, such as spironolactone or other potassium-sparing diuretics, may be initiated or increased to control persistent hypokalemia and associated elevated BP or edema. If daily oral potassium replacement, mineralocorticoid receptor antagonism, or other potassium-sparing diuretics are insufficient, the CORT125134 dose can be decreased to the lower dose, if applicable, or study drug should be discontinued if the patient is on the lowest dose of CORT125134. If oral administration of potassium is not feasible or cardiac complications of hypokalemia exist, intravenous potassium replacement may be required and may necessitate cardiac telemetry.

7.14.4.3 Hypertension

Patients who develop hypertension while on study drug should have the diagnosis confirmed by ambulatory BP monitoring. In addition, the patient should be examined for edema and potassium levels should be checked.

7.15 Early Study Discontinuation

If a patient withdraws from the study before completing the Week 12 visit, he or she should be asked to return for an ET visit, at which all Week 12 assessments (Section 8.14) will be performed.

The patient will be asked to also return for a follow-up visit 4 weeks after the ET visit has been completed. In both Group 1 and Group 2, patients who discontinue study early may be replaced to ensure that:

- 12 patients per group provide steady-state PK data through Week 10
- 15 patients provide safety and efficacy data through Week 10.

The Medical Monitor should be notified of patient discontinuations from the study.

7.16 Removal of Patients from Treatment or Assessment

Study drug treatment will be discontinued early if any of the following events occur:

- Evidence of excessive GR blockade based on a combination of the following Grade 3 or higher events: fatigue, anorexia, nausea and vomiting (associated with decreased oral intake), and abdominal pain, seen either at the 100-mg dose level or at other dose levels for which the investigator deems dose reduction is not an option (refer to Section 7.14.4.1 for monitoring for excessive glucocorticoid receptor blockade)
- Uncontrolled hypertension, defined as systolic BP >170 mmHg or diastolic BP >110 mmHg (as confirmed by ambulatory blood pressure monitoring) despite the use of appropriate antihypertension medications.

- Severe (<2.5 mEq/L) hypokalemia and/or persistent hypokalemia that does not respond to replacement of potassium and MR antagonists or other potassium sparing diuretics. Confirmed QTcF >500 ms. If QTcF is >500 ms, another ECG should be repeated within 24 hours and after any coexistent electrolyte abnormality is corrected. If a medication known to cause QTc prolongation has been started, it should be discontinued and the ECG should be repeated. If QTc prolongation persists, based on the average of at least 2 ECGs, the patient should be discontinued.
- [redacted]

THE DRC WILL BE NOTIFIED OF ALL
SERIOUS ADVERSE EVENTS AND DISCONTINUATIONS

8 PROCEDURES

A schedule of events is provided in Appendix 13.1.

Most assessments are for all patients; a few are performed only in patients in a specific subgroup. Note that a patient can be in the impaired glucose tolerance/diabetes subgroup, the hypertension subgroup, or both.

For patients who roll over from Group 1 to Group 2:

- There will not be a treatment completion visit in between Group 1 and Group 2 study visits.
- The Week 12 visit will serve as the new baseline visit for the Group 2 treatment period
- The safety follow-up visit for Group 1 (Week 16) is not necessary

8.1 Screening (Day −42 to Day −1)

Note: Patients requiring washout of a medication for Cushing's syndrome must complete the screening/baseline 24-hour UFC tests, salivary cortisol tests, oGTTs, and 24-hour ambulatory BP monitoring tests after a minimum washout of 2 weeks for adrenostatic medications and short-acting somatostatin analogs, 4 weeks for mifepristone and dopamine agonists, and 6 weeks for long-acting somatostatin ligands and within 3 weeks before Day 1 dosing.

Patients rolling from Group 1 to Group 2 do not require these assessments, and the screening visit will not be repeated between participation in Group 1 and Group 2.

- Informed consent
- Demographics and baseline disease characteristics
- Medical history and medication history
- Height
- Inclusion/exclusion criteria
- DST (if warranted for study entry). A DST done within 12 weeks before the ICF is signed will be accepted.
- Body weight
- 24-hour UFC with creatinine (collected by the patient at home at least two times and up to four times during screening). The average of the results will serve as "baseline".
- Urinary calcium (Ca), sodium (Na) from 24-hour UFC
- Salivary cortisol (collected by the patient at home at least two times and up to four times on different nights during screening). For screening, the average of the results will serve as "baseline".
- 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.
- Menstrual cycle information (premenopausal women not taking hormonal birth control)
- Complete physical examination
- Vital signs, including BP, heart rate, respiratory rate, and oral body temperature
- 12-lead ECG

- AEs
- Concomitant medications record
- Blood samples for
  - 2-hour oGTT (after an 8-hour fast)
  - HbA1c (value within 3 months of Day 1 dose)
  - HPA axis tests (ACTH, serum cortisol, 17-OH-progesterone, 11-deoxycortisol, DHEA-S, and androstenedione)
  - Pregnancy test (female patients)
  - Chemistry, thyroid, and hematology tests

Patients who fail screening may be rescreened (see Section 4.3).

Pituitary MRI radiographic scans and assessments in patients with Cushing disease that are obtained up to 6 months before Day 1 as standard of care will be collected if available.

8.2 Baseline Visit (Day 1)

Note: for patients rolling from Group 1 to Group 2, the Week 12 assessments in Group 1 equal the baseline visit assessments in Group 2.

Predose assessments include:

- Inclusion/exclusion criteria
- Enrollment
- Body weight
- Waist circumference
- BDI-II
- Trail making test
- CushingQoL questionnaire
- Sit-to-stand test
- Menstrual cycle information (premenopausal women not taking hormonal birth control)
- Complete physical examination
- Vital signs, including BP, heart rate, respiratory rate, and oral body temperature
- AEs
- Concomitant medications
- Physician's Global Assessment
- Blood samples for
  - 2-hour oGTT (after an 8-hour fast; impaired glucose tolerance/diabetes subgroup only)
  - HbA1c
  - Fructosamine
  - Adiponectin
  - Lipid panel
  - Sex hormone levels
  - Coagulation panel

  - GR activity biomarkers
  - HPA axis tests (ACTH, serum cortisol, 17-OH-progesterone, 11-deoxycortisol, DHEA-S, and androstenedione)
  - ACTH precursors
  - High-sensitivity C-reactive protein
  - IGF-1
  - Chemistry, thyroid, and hematology tests
  - Bone laboratory parameters
- Urine samples for
  - Urine pregnancy test (female patients only)
  - Bone laboratory parameters
- Administration of the Day 1 dose of study drug ***after*** completion of all baseline tests
- Study drug dispensing (2-week supply of study drug)
- Patient diary card dispensed

8.3 Week 1: Study Day 7 (± 1 day) – Telephone or Email Contact

Study drug compliance, AEs, and concomitant medication changes will be captured.

8.4 Week 2: Study Day 14 (± 2 days)

- Compliance check
- 24-hour UFC with creatinine (collected by the patient two times at home within 1 week prior to the study visit)
- Urinary Ca, Na from 24-hour UFC
- Salivary cortisol (collected by the patient two times at home within 1 week prior to the study visit)
- 24-hour ambulatory BP test (hypertension subgroup only; initiated in the clinic and completed by the patient at home)
- Body weight
- Menstrual cycle information (premenopausal women not taking hormonal birth control)
- Complete physical examination
- Vital signs, including BP, heart rate, respiratory rate, and oral body temperature
- AEs
- Concomitant medications
- Physician's Global Assessment
- Blood samples for
  - Serial PK: predose and 1, 2, 4, 6, and 8 hours postdose
  - Fructosamine
  - HPA axis tests (ACTH, serum cortisol, 17-OH-progesterone, 11-deoxycortisol, DHEA-S, and androstenedione)
  - ACTH precursors
  - Chemistry, thyroid, and hematology tests

- Urine sample for
  - Urine pregnancy test (female patients only)
- Administration of the daily dose of study drug
- 12-lead ECG (2 hours ± 30 min after study drug dosing)
- Study drug dispensing (2-week supply of study drug)
- Patient diary collected, reviewed and a new diary card dispensed

8.5 Week 3: Study Day 21 (± 1 day) – Telephone or Email Contact

Study drug compliance, AEs, and concomitant medication changes will be captured.

8.6 Week 4: Study Day 28 (± 2 days)

- Compliance check
- 24-hour UFC with creatinine (collected by the patient two times at home within 1 week prior to the study visit)
- Urinary Ca, Na from 24-hour UFC
- Salivary cortisol (collected by the patient two times at home within 1 week prior to the study visit)
- 24-hour ambulatory BP test (hypertension subgroup only initiated in the clinic and completed by the patient at home)
- Body weight
- Waist circumference
- BDI-II
- Trail making test
- CushingQoL questionnaire
- Sit-to-stand test
- Menstrual cycle information (premenopausal women not taking hormonal birth control)
- Complete physical examination
- Vital signs, including BP, heart rate, respiratory rate, and oral body temperature
- AEs
- Concomitant medications
- Physician's Global Assessment
- Blood samples for
  - 2-hour oGTT (after an 8-hour fast; impaired glucose tolerance/diabetes subgroup only)
  - Trough PK: predose only
  - Fructosamine
  - Adiponectin
  - Lipid panel
  - Coagulation panel
  - GR activity biomarkers
  - HPA axis tests (ACTH, serum cortisol, 17-OH-progesterone, 11-deoxycortisol, DHEA-S, and androstenedione)

  - ACTH precursors
  - High-sensitivity C-reactive protein
  - IGF-1
  - Chemistry, thyroid, and hematology tests
  - Bone laboratory parameters
- Urine samples for
  - Urine pregnancy test (female patients only)
  - Bone laboratory parameters
- Administration of the daily dose of study drug
- 12-lead ECG (2 hours ± 30 min after study drug dosing)
- Study drug dispensing (2-week supply of study drug)
- Patient diary collected, reviewed and a new diary card dispensed
- Medical Monitor approves dose escalation
- Dose escalation starts the day after the Week 4 visit

8.7 Week 5: Study Day 35 (± 1 day) – Telephone or Email Contact

Study drug compliance, AEs, and concomitant medication changes will be captured.

8.8 Week 6: Study Day 42 (± 2 days)

- Compliance check
- 24-hour UFC with creatinine (collected by the patient two times at home within 1 week prior to the study visit)
- Urinary Ca, Na from 24-hour UFC
- Salivary cortisol (collected by the patient two times at home within 1 week prior to the study visit)
- 24-hour ambulatory BP test (hypertension subgroup only; initiated in the clinic and completed by the patient at home)
- Body weight
- Menstrual cycle information (premenopausal women not taking hormonal birth control)
- Complete physical examination
- Vital signs, including BP, heart rate, respiratory rate, and oral body temperature
- AEs
- Concomitant medications
- Physician's Global Assessment
- Blood samples for
  - Serial PK: predose and 1, 2, 4, 6, and 8 hours postdose
  - Fructosamine
  - HPA axis tests (ACTH, serum cortisol, 17-OH-progesterone, 11-deoxycortisol, DHEA-S, and androstenedione)
  - ACTH precursors
  - Chemistry, thyroid, and hematology tests

- Urine sample for
  - Urine pregnancy test (female patients only)
- Administration of the daily dose of study drug
- 12-lead ECG (2 hours ± 30 min after study drug dosing)
- Study drug dispensing (2-week supply of study drug)
- Patient diary collected, reviewed and a new diary card dispensed

8.9 Week 7: Study Day 49 (± 1 day) – Telephone or Email Contact

Study drug compliance, AEs, and concomitant medication changes will be captured.

8.10 Week 8: Study Day 56 (± 2 days)

- Compliance check
- 24-hour UFC with creatinine (collected by the patient two times at home within 1 week prior to the study visit)
- Urinary Ca, Na from 24-hour UFC
- Salivary cortisol (collected by the patient two times at home within 1 week prior to the study visit)
- 24-hour ambulatory BP test (hypertension subgroup only; initiated in the clinic and completed by the patient at home
- Body weight
- Waist circumference
- BDI-II
- Trail making test
- CushingQoL questionnaire
- Sit-to-stand test
- Menstrual cycle information (premenopausal women not taking hormonal birth control)
- Complete physical examination
- Vital signs, including BP, heart rate, respiratory rate, and oral body temperature
- AEs
- Concomitant medications
- Physician's Global Assessment
- Blood samples for
  - 2-hour oGTT (after an 8-hour fast; impaired glucose tolerance/diabetes subgroup only)
  - Trough PK: predose only
  - Fructosamine
  - Adiponectin
  - Lipid panel
  - Coagulation panel
  - GR activity biomarkers
  - HPA axis tests (ACTH, serum cortisol, 17-OH-progesterone, 11-deoxycortisol, DHEA-S, and androstenedione)

  - ACTH precursors
  - High-sensitivity C-reactive protein
  - IGF-1
  - Chemistry, thyroid, and hematology tests
  - Bone laboratory parameters
- Urine samples for
  - Urine pregnancy test (female patients only)
  - Bone laboratory parameters
- Administration of the daily dose of study drug
- 12-lead ECG (2 hours ± 30 min after study drug dosing)
- Study drug dispensing (2-week supply of study drug)
- Patient diary collected, reviewed and a new diary card dispensed
- Medical Monitor approves dose escalation
- Dose escalation starts the day after the Week 8 visit

8.11 Week 9: Study Day 63 (± 1 day) – Telephone or Email Contact

Study drug compliance, AEs, and concomitant medication changes will be captured.

8.12 Week 10: Study Day 70 (± 2 days)

- Compliance check
- 24-hour UFC with creatinine (collected by the patient two times at home within 1 week prior to the study visit)
- Urinary Ca, Na from 24-hour UFC
- Salivary cortisol (collected by the patient two times at home within 1 week prior to the study visit)
- 24-hour ambulatory BP test (hypertension subgroup only; initiated in the clinic and completed by the patient at home)
- Body weight
- Menstrual cycle information (premenopausal women not taking hormonal birth control)
- Complete physical examination
- Vital signs, including BP, heart rate, respiratory rate, and oral body temperature
- AEs
- Concomitant medications
- Physician's Global Assessment
- Blood samples for
  - Serial PK: predose and 1, 2, 4, 6, and 8 hours postdose
  - Fructosamine
  - HPA axis tests (ACTH, serum cortisol, 17-OH-progesterone, 11-deoxycortisol, DHEA-S, and androstenedione)
  - ACTH precursors
  - Chemistry, thyroid, and hematology tests

- Urine sample for
  - Urine pregnancy test (female patients only)
- Administration of the daily dose of study drug
- 12-lead ECG (2 hours ± 30 min after study drug dosing)
- Study drug dispensing (2-week supply of study drug)
- Patient diary collected, reviewed and a new diary card dispensed

8.13 Week 11: Study Day 77 (±1 day) – Telephone or Email Contact

Study drug compliance, AEs, and concomitant medication changes will be captured.

8.14 Group 1, Week 12: Study Day 84/Early Termination (± 2 days)

If a patient discontinues from the study early (ET), all Week 12 assessments will be done at the time of termination or soon thereafter. For patients rolling over from Group 1 to Group 2, the Week 12 visit will serve as the baseline visit for their Group 2 treatment period.

- Compliance check
- 24-hour UFC with creatinine (collected by the patient at home within 1 week prior to the study visit)
- Urinary Ca, Na from 24-hour UFC
- Salivary cortisol (collected by the patient two times at home within 1 week prior to the study visit)
- 24-hour ambulatory BP test (hypertension subgroup only; initiated in the clinic and completed by the patient at home)
- Body weight
- Waist circumference
- BDI-II
- Trail making test
- CushingQoL questionnaire
- Sit-to-stand test
- Menstrual cycle information (premenopausal women not taking hormonal birth control)
- Complete physical examination
- Vital signs, including BP, heart rate, respiratory rate, and oral body temperature
- AEs
- Concomitant medications
- Physician's Global Assessment
- Patient diary collected and reviewed
- Blood samples for
  - 2-hour oGTT (after an 8-hour fast; impaired glucose tolerance/diabetes subgroup only)
  - Trough PK: predose only
  - HbA1c
  - Fructosamine
  - Adiponectin

  - Lipid panel
  - Sex hormone levels
  - Coagulation panel
  - GR activity biomarkers
  - HPA axis tests (ACTH, serum cortisol, 17-OH-progesterone, 11-deoxycortisol, DHEA-S, and androstenedione)
  - ACTH precursors
  - High-sensitivity C-reactive protein
  - IGF-1
  - Chemistry, thyroid, and hematology tests
  - Bone laboratory parameters
- Urine samples for
  - Urine pregnancy test (female patients only)
  - Bone laboratory parameters
- Administration of final dose of study drug (Week 12 Visit only)
- 12-lead ECG (this will be done 2 ± 30 mins hours after study drug dosing)

8.15 Group 2, Week 12: Study Day 84 (± 2 days)

- Compliance check
- 24-hour UFC with creatinine (collected by the patient two times at home within 1 week prior to the study visit)
- Urinary Ca, Na from 24-hour UFC
- Salivary cortisol (collected by the patient two times at home within 1 week prior to the study visit)
- 24-hour ambulatory BP test (hypertension subgroup only; initiated in the clinic and completed by the patient at home
- Body weight
- Waist circumference
- BDI-II
- Trail making test
- CushingQoL questionnaire
- Sit-to-stand test
- Menstrual cycle information (premenopausal women not taking hormonal birth control)
- Complete physical examination
- Vital signs, including BP, heart rate, respiratory rate, and oral body temperature
- AEs
- Concomitant medications
- Physician's Global Assessment
- Blood samples for
  - 2-hour oGTT (after an 8-hour fast; impaired glucose tolerance/diabetes subgroup only)
  - Trough PK: predose only

  - HbA1c
  - Fructosamine
  - Adiponectin
  - Lipid panel
  - Coagulation panel
  - GR activity biomarkers
  - HPA axis tests (ACTH, serum cortisol, 17-OH-progesterone, 11-deoxycortisol, DHEA-S, and androstenedione)
  - ACTH precursors
  - High-sensitivity C-reactive protein
  - IGF-1
  - Chemistry, thyroid, and hematology tests
  - Bone laboratory parameters
- Urine samples for
  - Urine pregnancy test (female patients only)
  - Bone laboratory parameters
- Administration of the daily dose of study drug
- 12-lead ECG (2 hours ± 30 min after study drug dosing)
- Study drug dispensing (2-week supply of study drug)
- Patient diary collected, reviewed and a new diary card dispensed
- Medical Monitor approves dose escalation
- Dose escalation starts the day after the Week 12 visit

8.16 Group 2, Week 13: Study Day 91 (±1 day) – Telephone or Email Contact

Study drug compliance, AEs, and concomitant medication changes will be captured.

8.17 Group 2, Week 14: Study Day 98 (± 2 days)

- Compliance check
- 24-hour UFC with creatinine (collected by the patient two times at home within 1 week prior to the study visit)
- Urinary Ca, Na from 24-hour UFC
- Salivary cortisol (collected by the patient two times at home within 1 week prior to the study visit)
- 24-hour ambulatory BP test (hypertension subgroup only; initiated in the clinic and completed by the patient at home)
- Body weight
- Menstrual cycle information (premenopausal women not taking hormonal birth control)
- Complete physical examination
- Vital signs, including BP, heart rate, respiratory rate, and oral body temperature
- AEs
- Concomitant medications
- Physician's Global Assessment

- Blood samples for
  - Serial PK: predose and 1, 2, 4, 6, and 8 hours postdose
  - Fructosamine
  - HPA axis tests (ACTH, serum cortisol, 17-OH-progesterone, 11-deoxycortisol, DHEA-S, and androstenedione)
  - ACTH precursors
  - Chemistry, thyroid, and hematology tests
- Urine sample for
  - Urine pregnancy test (female patients only)
- Administration of the daily dose of study drug
- 12-lead ECG (2 hours ± 30 min after study drug dosing)
- Study drug dispensing (2-week supply of study drug)
- Patient diary collected, reviewed and a new diary card dispensed

8.18 Group 2, Week 15: Study Day 105 (±1 day) – Telephone or Email Contact

Study drug compliance, AEs, and concomitant medication changes will be captured.

8.19 Group 2, Week 16: Study Day 112/Early Termination (± 2 days)

If a Group 2 patient discontinues from the study early (ET), all Week 16 assessments will be done at the time of termination or soon thereafter.

- Compliance check
- 24-hour UFC with creatinine (collected by the patient at home within 1 week prior to the study visit)
- Urinary Ca, Na from 24-hour UFC
- Salivary cortisol (collected by the patient two times at home within 1 week prior to the study visit)
- 24-hour ambulatory BP test (hypertension subgroup only; initiated in the clinic and completed by the patient at home)
- Body weight
- Waist circumference
- BDI-II
- Trail making test
- CushingQoL questionnaire
- Sit-to-stand test
- Menstrual cycle information (premenopausal women not taking hormonal birth control)
- Complete physical examination
- Vital signs, including BP, heart rate, respiratory rate, and oral body temperature
- AEs
- Concomitant medications
- Physician's Global Assessment
- Patient diary collected and reviewed
- Blood samples for

  - 2-hour oGTT (after an 8-h fast; impaired glucose tolerance/diabetes subgroup only)
  - Trough PK: predose only
  - HbA1c
  - Fructosamine
  - Adiponectin
  - Lipid panel
  - Sex hormone levels
  - Coagulation panel
  - GR activity biomarkers
  - HPA axis tests (ACTH, serum cortisol, 17-OH-progesterone, 11-deoxycortisol, DHEA-S, and androstenedione)
  - ACTH precursors
  - High-sensitivity C-reactive protein
  - IGF-1
  - Chemistry, thyroid, and hematology tests
  - Bone laboratory parameters
- Urine samples for
  - Urine pregnancy test (female patients only)
  - Bone laboratory parameters
- Administration of final dose of study drug (Week 16 Visit only)
- 12-lead ECG (this will be done 2 hours ± 30 min after study drug dosing)

8.20 Group 1, Follow-up Visit at Week 16: Study Day 112 (+7 days) and Group 2, Follow-up Visit at Week 20: Study Day 140 (+7 days)

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

- Body weight
- Waist circumference
- CushingQoL questionnaire
- Complete physical examination
- Vital signs, including BP, heart rate, respiratory rate, and oral body temperature
- 12-lead ECG
- AEs
- Concomitant medications
- Physician's Global Assessment
- Blood samples for
  - Lipid panel
  - Chemistryand hematology tests
- Urine sample for
  - Urine pregnancy test

Pituitary MRI radiographic scans and assessments in patients with Cushing disease that are obtained up to 1 month after last CORT125134 dose as standard of care will be collected if available.

9 QUALITY CONTROL AND ASSURANCE

This study will be performed and reported in compliance with Good Clinical Practice (GCP), the protocol, applicable standard operating procedures, and applicable regulations. To ensure compliance, the Sponsor may conduct a quality assurance audit.

Prior to selection of the study site(s), a site evaluation visit(s) will be performed to review the adequacy of the facility (ies), personnel, and their ability to conduct research. A site initiation visit and/or Investigator's meeting will be held prior to study start-up to train the Investigators and study coordinators on the protocol, source document and eCRF completion, safety, study drug handling, sample handling, and to review GCP.

This study will use eCRFs designed to allow capture and recording of all protocol-required information for each patient. All eCRFs will be completed by the clinic staff, and all completed eCRFs will be reviewed by the Principal Investigator, as noted by his or her electronic signature, prior to review by the clinical monitor or designated representative. The clinical monitor or designated representative will review all source records on site and compare them to the data collected on the eCRF.

Data will be entered into a clinical database as specified in the Sponsor's/contract research organization's data management plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database. Data will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification will be communicated to the investigational site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections will be documented in an audit trail.

Assay of clinical safety laboratory samples and any other samples will be performed by certified laboratories using validated analytical methods.

10 PLANNED STATISTICAL METHODS

10.1 General Considerations

The statistical analysis will be conducted by the Sponsor and/or its designee. Statistical methods will be prespecified and documented in detail in a Statistical Analysis Plan, to be finalized prior to database lock.

All summaries will be presented by starting dose group, regardless of the actual dose level at the time point associated with the data collection. In addition, data will be tabulated for all patients combined. All relevant data collected on the eCRF will be presented in by-patient data listings, to include the site identifier, patient number, and starting dose group. Listing presenting study data over time will include the dose level the patient received at the time of data collection. In addition to summary tables by dosing group and by-patient data listings, individual patient profiles will be generated to list and display graphically key study endpoints over time.

In general, continuous variables will be summarized by the number of patients with non-missing data, mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized by the number and percentage of patients in each category.

Predose measurements on Day 1 will be considered the primary baseline values. If a Day 1 predose value is not available, the screening measurement may be used as the baseline value. Select analyses may also assess changes from the last measurement prior to escalation to the current dose level received. Additionally, patients in Group 1 who continue treatment as part of Group 2 may have data collected while receiving Group 2 dosing summarized as a change relative to their last measurement collected prior to dosing as part of Group 1 (ie, the Group 1 baseline value).

10.2 Analysis Population

The analysis population for all efficacy and safety analyses will include all patients who received at least one dose of study drug. As defined in the PK analysis plan, the PK analysis population will comprise all patients who have evaluable PK data.

For all analyses, the patient will be included in the dose group in which he or she was enrolled, regardless of actual dose level at the time point when the data were collected.

Select efficacy endpoints will be analyzed by subgroup only:

- Patients with impaired glucose tolerance/diabetes
- Patients with hypertension

All enrolled patients will belong to at least one of these subgroups and an individual patient may be included in both. If a patient enters the study with hypertension but takes an additional antihypertensive medication or increases the dosage of a concurrent antihypertensive medication, that patient will be classified as a nonresponder (see Section 10.6 for definition of response for each subgroup). If a patient enters the study with diabetes/impaired glucose tolerance but takes an additional diabetes medication or increases the dosage of a concurrent diabetes medication, that patient will be classified as a nonresponder.

10.3 Patient Disposition

Patient disposition information will be summarized by dose group and overall. Summaries will include the number of enrolled patients, the number of patients in each analysis population, the number of patients in each subgroup, the number of patients completing the study per protocol, and the number of patients terminating the study early by the primary reason for discontinuation.

10.4 Demographic and Baseline Characteristics

Demographic variables will include age at the time of informed consent, sex, ethnicity and race. Other baseline characteristics will include relevant medical history and baseline disease characteristics (eg, time since diagnosis, Cushing's syndrome type). Demographic and baseline characteristics will be summarized for all treated patients and presented separately by subgroup, by dose group, and overall.

10.5 Concomitant Medications

Verbatim terms on eCRFs will be mapped to Anatomical/Therapeutic Chemical class and Generic Drug Names using the most current version of the World Health Organization Drug Dictionary. Concomitant medications will be summarized for all treatment patients by dose group and overall.

10.6 Efficacy Analyses

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

Responder endpoints for each subgroup as defined below will be summarized separately for the following patient analysis sets:

- Group 1 patients, where responder status is determined based on the Group 1 baseline value;
- Group 2 patients, where responder status is determined based on the Group 2 baseline value;
- Group 2 patients, where responder status is determined based on the Group 1 baseline value for those patients who were also enrolled and treated in Group 1, and the Group 2 baseline value for those patients who were not enrolled in Group 1;
- Group 2 patients who were not enrolled and treated in Group 1, where responder status is determined based on the Group 2 baseline value;
- Group 2 patients who were also enrolled and treated in Group 1, where responder status is determined based on the Group 2 baseline value.

10.6.1 Impaired Glucose Tolerance/Diabetes Subgroup

The area under the concentration-time curve for glucose ($AUC_{glucose}$) will be calculated based on results of the oGTTs from baseline to Week 12/ET in Group 1 or Week 16/ET in Group 2, for those patients with impaired glucose tolerance or diabetes at study entry. 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. The number and percentage of patients who are responders will be presented by dose group and for all patients, along with the 95% binomial exact confidence interval.

$AUC_{glucose}$ will be summarized by descriptive statistics by dose group and for all patients. In addition, plasma glucose, HbA1c, fructosamine, and adiponectin concentrations will be summarized using descriptive statistics by visit, time point, and dose group, to include the change from baseline and change from the last measurement collected prior to escalation to the current dose level at each visit and time point. Plots of the mean plasma glucose values over time will be presented.

The number and percentage of patients whose dose of medications that lower blood glucose decreased, stayed the same, or increased from baseline to Week 12/ET in Group 1 or Week 16/ET in Group 2 will be summarized, among those patients taking such medications at baseline.

10.6.2 Hypertension Subgroup

Changes in mean diastolic BP and systolic BP measured by 24-hour ambulatory BP monitoring will be analyzed for patients with hypertension at study entry. A responder will be defined as a patient who experiences at least a 5 mmHg decrease in mean diastolic or systolic BP from baseline to Week 12/ET in Group 1 or Week 16/ET in Group 2 who has not taken an additional antihypertensive medication during the treatment period or increased the dosage of a concurrent antihypertensive medication. The number and percentage of patients who are responders will be presented by dose group and for all patients, along with the 95% binomial exact confidence interval.

Diastolic and systolic BP will be summarized using descriptive statistics by visit, time point, and dose group, to include the change from baseline and change from the last measurement collected prior to escalation to the current dose level at each visit and time point.

The number and percentage of patients whose dose of antihypertensive medication decreased, stayed the same, or increased from baseline to Week 12/ET in Group 1 or Week 16/ET in Group 2 will be summarized, among those patients taking such medications at baseline.

10.6.3 Other Measures of Efficacy

Other measures of efficacy will be summarized for all patients receiving treatment, regardless of indication at study treatment, by dose group, and for all patients.

Results for efficacy variables from data collection, including body weight and body composition by quality of life, 24-hour UFC, salivary cortisol, strength scores, lipid panel, coagulation, hormonal and menstrual cycle, bone laboratory parameters, and high-sensitivity C-reactive protein will be summarized using descriptive statistics by parameter, visit, and time point, to include the changes from baseline.

10.7 Pharmacokinetic Analyses

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

10.8 Safety Analyses

Adverse events will be mapped to system organ classes and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs are defined as those that start or worsen after the start of study treatment and up to 28 days after the last dose of study treatment.

Treatment-emergent AEs will be summarized overall and by dose group and displayed by system organ class and preferred term. Treatment-emergent AEs will be further summarized by severity and relationship to study treatment. At each level of summation, patients will be counted only once, under the greatest severity and strongest study-drug relationship (as reported by the Investigator).

All AEs (whether TEAEs or not) will be listed by individual patient, including information regarding onset, duration, severity, and relationship to study drug. Serious AEs and AEs that led to withdrawal from the study will be listed by individual patient.

Clinical laboratory test results (chemistry and hematology), vital sign measurements, and ECG interval results will be summarized overall and for each dose group by parameter, visit, and time point using descriptive statistics, to include the change from baseline values. Shift tables will be constructed that describe changes from baseline to the end of treatment in clinical laboratory values.

10.9 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 and to establish point estimates for efficacy endpoints for future evaluation of the study drug.

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Institutional Review Board/Independent Ethics Committee

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The Investigator must submit written approval to the Sponsor, before he or she can enroll any patient into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

11.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, and applicable regulatory requirements.

The Principal Investigator will ensure that the study procedures outlined in this protocol will be conducted in accordance with the US Code of Federal Regulations (CFR) governing Protection of Human Subjects (21 CFR 50), Financial Disclosure by Clinical Investigators (21 CFR 54), IRBs (21 CFR 56), Investigational New Drug Application (21 CFR 312), and Applications for Food and Drug Administration Approval to Market a New Drug (21 CFR 314), as appropriate.

11.3 Patient Informed Consent

The Principal Investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The ICF will contain all of the elements required by ICH guidelines for GCP and any additional elements required by local regulations.

The ICF must include information about the possible retention of biological samples at the conclusion of this study; with the patient's permission, samples may be retained for future determination of active metabolite concentrations and possible biomarkers related to drug response.

The patient's signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient.

11.4 Patient Confidentiality

To maintain patient privacy, all source documents, study reports, and communications will identify the patient by initials and the assigned patient number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority (ies) access to the patient's original study records for verification of data gathered on source documents and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by applicable laws and regulations.

11.5 Study Monitoring

Monitoring of the study site (including, but not limited to, reviewing eCRFs for accuracy and completeness, and assessing compliance with the protocol and adherence to regulatory and GCP requirements) will be performed by the Sponsor's Clinical Monitor or designee. Monitoring will be performed in accordance with applicable federal regulations and guidance. Monitoring methods, responsibilities, and requirements will be outlined in a monitoring plan.

11.6 Case Report Forms and Study Records

The Investigator must generate and maintain adequate and accurate records to enable full documentation of study conduct. Study data will be captured on eCRFs. Investigators must retain all original source documents.

11.7 Access to Source Documentation

The Sponsor or its representative will be allowed to conduct site visits to the investigational facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and source documents, and other records relative to study conduct.

By signing the protocol, the Principal Investigator agrees that, within local regulatory restrictions and institutional and ethical considerations, authorized representatives of the Sponsor, a regulatory authority, and/or an IRB/IEC may visit the site to perform audits or inspections, including the drug storage area, study drug stocks, drug accountability records, patient charts and source documents, and other records relative to study conduct. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents (eg, laboratory reports, x-rays, workbooks, patients' medical records) to determine whether these activities were conducted, and data recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements.

The Investigator should contact the Sponsor immediately if contacted by a regulatory agency regarding an inspection.

11.8 Protocol Deviations

The Investigator should not implement any deviation from the protocol without prior review and agreement by the Sponsor and in accordance with the IEC/IRB and local regulations, except when necessary to eliminate an immediate hazard to study patients. When a deviation from the protocol is deemed necessary for an individual patient, the Investigator must contact the Medical

Monitor. Such contact must be made as soon as possible to permit a review by the Sponsor to determine the impact of the deviation on the patient and/or the study. Any significant protocol deviations affecting patient eligibility and/or safety must be reviewed and/or approved by the IEC/IRB and regulatory authorities, as applicable, prior to implementation.

11.9 Records Retention

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for the Sponsor or the regulatory authority to review any documentation relating to the study, the Investigator must permit access to such records.

11.10 Financial Disclosure

Investigators will be required to disclose any financial equity interests in the Sponsor and any conflicts of interest, as defined by the Sponsor.

11.11 Publication and Disclosure Policy

Corcept as the Sponsor, has a proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple Investigators and sites and Corcept personnel. Authorship will be established before writing of the manuscript. Because this study involves multiple centers, no individual publications will be allowed before completion of the final report of the multicenter study except as agreed with Corcept.

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13 APPENDICES

13.1 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	
Menstrual cycle information [m]	X	X		X		X		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
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	X	X		X		X		X		X		X		X	X
Chemistry and hematology	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's syndrome are prohibited and require washout (as applicable) during screening provided the intervals specified in Exclusion Criterion 14 fit within the screening window. Patients requiring washout of a medication for Cushing's 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's 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 lipoprotein-cholesterol, high-density lipoprotein-cholesterol, 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 thrombin-antithrombin.

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.

13.2 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	

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
Sex hormone levels [n]		X														X	
Coagulation panel [o]		X				X				X				X		X	
GR activity biomarkers test		X				X				X				X		X	
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 C-reactive 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's syndrome are prohibited and require washout (as applicable) during screening provided the intervals specified in Exclusion Criterion 14 fit within the screening window. Patients requiring washout of a medication for Cushing's 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's 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 lipoprotein-cholesterol, high-density lipoprotein-cholesterol, 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 thrombin-antithrombin.

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).

13.3 Study Patient Identification Card

At study enrollment, all patients will be given a card to carry with them that identifies their potential risk for excessive GR blockade. A copy of the card is provided below:

CORT125134-451 Study Participant Information Card

_____is a participant in a clinical trial for Cushing's syndrome.

Name

This participant was, and may still be, receiving CORT125134, a glucocorticoid antagonist which blocks the effects of the hormone cortisol. This individual may be at increased risk for the development of excessive glucocorticoid receptor (GR) blockade. He/She may require supplemental treatment with glucocorticoids in the setting of shock, surgery, or serious illness or injury (eg, infection, fracture, bleeding). In such cases, administration of dexamethasone (4–10 mg intravenously or intramuscularly), fluid resuscitation, and supportive medical care should be administered. Additional glucocorticoid should be continued and adjusted according to the clinical course.

In case of suspected excessive GR blockade, please contact the investigator/study physician immediately at:

_____

Phone number

_____

Name of Investigator

13.4 Summary of Changes in Protocol CORT125134-451 Version 7.0

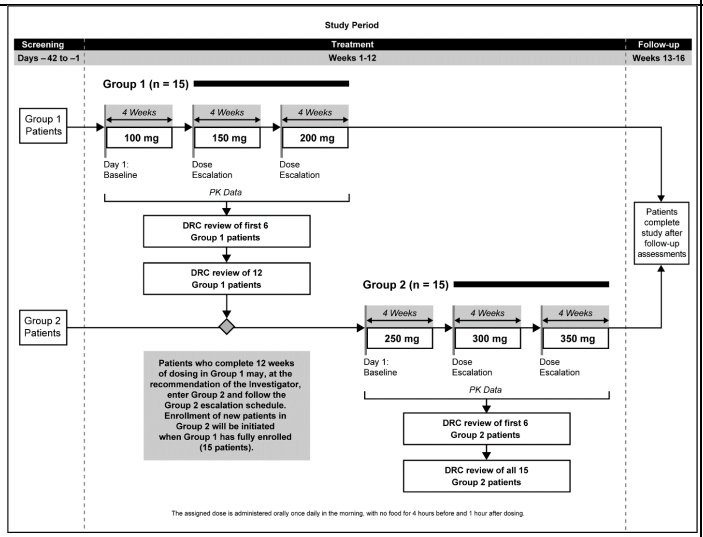
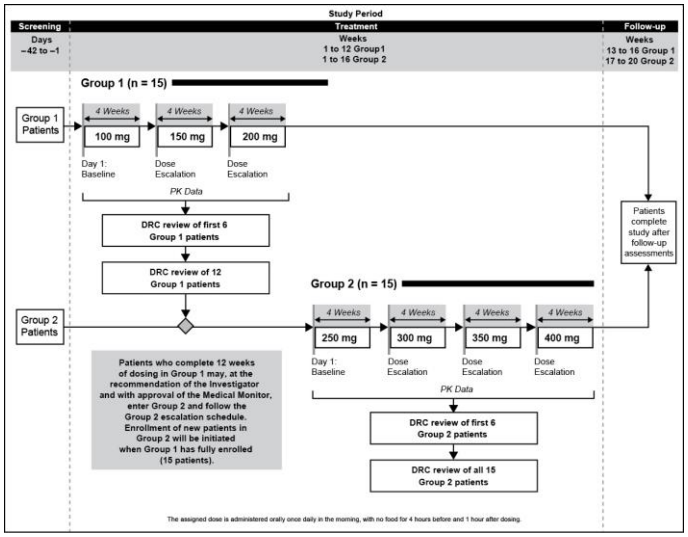
Significant changes in Version 7.0 of the protocol (dated 15 January 2018) compared with Version 6.0, dated 16 November 2016) are summarized in Table 7. The major change is the addition of the 400-mg CORT125134 dose level that adds 4 more weeks of treatment to Group 2.

Minor editorial or stylistic changes made for consistency, correction of typographical errors, and use of abbreviations are not summarized. Deleted text is shown as a ~~strikethrough~~ and new text is shown in **bold font**.

Table 7 Summary of Changes in Protocol CORT125134-451 Version 7

Section	Revision	Rationale
Global changes *shown* in the redline version	Version 6.0 was changed to Version 7.0 with updated date.	Administrative change
	In version 7.0, a fourth dose level (ie, 400 mg CORT125134 daily for 4 weeks) was added to the Group 2 dose levels such that dose escalation increases in 50-mg increments from 250 mg to 400 mg. This addition required changes throughout the protocol, including the following: • The study rationale (Section 1) • The lists of assessments (especially Section 7 and Section 8 and the Schedule of Assessments): – The addition of 4 weeks of CORT125134 treatment to all descriptions of Group 2 dosing and administration (eg, the addition of "then 400 mg/day for 4 weeks" to "250 mg/day for 4 weeks, then 300 mg/day for 4 weeks, then 350 mg/day for 4 weeks") – The addition of the assessment time points for Group 2 (eg, "For Group 2, 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.") – The addition of new subsections in Section 8 Procedures that outline activities for Group 2 Weeks 12–16 – A new, separate table in Appendix 13.2 to show the schedule of assessments for Group 2 • Extension of the study duration from "up to 34 weeks" to "up to 38 weeks" • Extension of the study treatment period from "up to 24 weeks" to "up to 28 weeks"	[redacted] The 400-mg dose was [redacted] endorsed by the 2nd DRC meeting.
Global changes that are *not shown* in the redline version	In Section 7, where assessments were stated to occur on "the Week 2, Week 4, Week 6, Week 8, Week 10, and Week 12/ET visits", the text was changed to "Weeks 2, 4, 6, 8, 12, and 12/ET" to improve readability.	Editorial changes

Section	Revision	Rationale
	The International Nonproprietary Name "relacorilant" was added to the cover page. Where appropriate, "subject" was changed to "patient". All section numbers, figure numbers, and table numbers were revised to reflect the additions and revisions in the text. Minor stylistic (eg, formatting) and editorial changes (eg, punctuation) were made.	
Synopsis: Study Period	Modified text Up to ~~34~~**38** weeks, including up to 6 weeks for screening, up to ~~24~~**28** weeks of treatment, and 4 weeks of follow-up	Extended the study period to allow patients in Group 2 to escalate to 400 mg CORT125134
Synopsis: Duration of Treatment	Updated the duration of treatment: Up to ~~24~~**28** weeks	Extended the treatment period to allow patients in Group 2 to escalate to 400 mg CORT125134
Synopsis: Study Design and Methodology	Updated Table S1. [redacted] The changes made in Table 3 were also made in Table S1.	[redacted]
Synopsis: Study Design and Methodology, Section 3.1 Overview of Study Design	Text for the following two bullets were updated: • Group 2: ~~projected doses are~~ CORT125134 250 mg/day for 4 weeks, then 300 mg/day for 4 weeks, then 350 mg/day for 4 weeks**, then 400 mg/day for 4 weeks**. Patients who discontinue prior to Week 10 may be replaced to ensure that at least 12 patients provide serial PK data through Week 10 in Group 1 and Group 2. • The DRC will also meet during Group 2, when steady-state PK data ~~at Week 10~~ are available for 6 patients**, who have reached their highest CORT125134 dose (ie, Week 10 if 350 mg and Week 14 if 400 mg)** and at the end of the study. Text describing the timing of patient visits for Group 2 was added.	Updated to include the 400-mg dose level in Group 2
	Updated the study design figure. Prior version of study design figure:	Updated to include the 400-mg dose level in Group 2

Section	Revision	Rationale
	 Updated version of study design figure: 	
Synopsis, Section 4.1 Inclusion Criteria 1, 4, 8, and 11 Also Section 7.12.4 Pregnancy Tests and Contraception Methods	Modified the following inclusion criteria: 1. Is a male or female adult, 18–~~75~~80 years of age 4. Meets at least one of the following criteria: Has impaired glucose tolerance (2-hour oGTT result for plasma glucose in the range of ≥140 mg/dL to <200 mg/dL) (Standards of Medical Care in Diabetes – 2015)	Extended age range at study entry from 75 to 80 years to allow enrollment of older patients Correction in plasma glucose range from >140 mg/dL to ≥140 mg/dL

Section	Revision	Rationale
	8. Female patients of childbearing potential must be willing to use a highly effective method of contraception from 30 days prior to Day 1 until 30 days after the last dose of study drug. Male patients with a female partner must agree to 2 forms of contraception, one of which must be a **double**-barrier method, from Day 1 until 30 days after the last dose of study drug. Highly effective methods of contraception include abstinence, oral contraceptives combined with a barrier method, diaphragm with vaginal spermicide, intrauterine device, condom and partner using vaginal spermicide, and surgical sterilization (≥6 months postsurgery).	Clarification
	11. Is able to participate in the study for up to 22 weeks **in Group 1 and 26 weeks in Group 2**, including returning to the investigative site to fulfill the safety and efficacy evaluations outlined in the protocol	Updated to include the 400-mg dose level in Group 2
Sections 1.1.2, 1.3.1, and 1.3.2	[redacted]	
Section 1.1.2 Clinical Experience: Safety	The following changes were made: [redacted] *Text in boldface was added:* [redacted]	[redacted]

Section	Revision	Rationale
	[redacted]	
Section 1.3.1 [redacted]	Updated the number of cohorts from 3 to 4. [redacted]	[redacted]

Section	Revision	Rationale
	[redacted]	
Section 1.3.2 [redacted]	[redacted]	[redacted]
3.1 Overview of Study Design	Added a new subheading	Added for cross-referencing
3.2 Data Review Committee	The following bullet was modified: • For oversight of Group 2: – When 6 evaluable patients have escalated to Dose 3 ~~of~~ **or 4 (whichever is the patient's highest** Group 2 **dose)** and PK and safety data are available	Revised to address inclusion of the 400-mg dose level

Section	Revision	Rationale
	– At end of study	
5.4.1 Dosing Groups and Dose Escalation	Modified text as needed to include the 400-mg CORT125134 dose level, and added a column to the tabulation to show the dose and number of capsules. [redacted]	Revised to address inclusion of the 400-mg dose level
7.5 Pituitary Magnetic Resonance Imaging (MRI) Scans	This new subsection was added with the following text: **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 as standard of care will be collected if available.**	Added to capture changes in pituitary MRI scans if the scans were performed as standard of care.
7.12.2 Vital Sign Measurements	Deleted "hypertensive" in the following sentence: In addition to the safety vital signs collected, a 24-hour ambulatory BP test will also be done by all ~~hypertensive~~ patients at screening and by patients in the hypertension subgroup at post-screening time points to assess the effect of CORT125134 on BP (see Section7.11.1.1).	Correction; all patients undergo ABPM at screening
7.12.5.2 Sample Collection, Storage, and Shipment	The following changes were made: The total volume of blood to be collected from each patient will be no more than ~~850~~ **731** mL for **Group 1 and 908 mL for Group 2 during the 12-week and 16-week** ~~each 12-week~~ treatment period.	Correction and revision to add the new value for the 400-mg treatment period.
7.13 Pregnancy	The following prior pregnancy section was deleted: 7.12.6.10 Pregnancy Pregnancy is not considered an AE, although a patient will be withdrawn from the study if a pregnancy occurs and the ET visit will be completed. The pregnancy must be immediately reported to the Sponsor and Medical Monitor. Additional follow-up may be required The following new subsection was added: 7.13 Pregnancy All pregnancies with the estimated date of conception occurring during the study treatment or within 30 days of the last dose of study treatment should be reported immediately to the Sponsor or its designee. The patient will be followed to determine the outcome of the pregnancy, and the outcome will be reported. 7.13.1 Maternal Exposure If a patient becomes pregnant during the study, the study treatment should be discontinued immediately. Pregnancy itself is not regarded as an AE. If a pregnancy occurs during the study treatment or within 30 days of the last dose of study treatment, the Investigator	The subsection was made a separate section from AEs because pregnancy is not considered to be an AE. The guidance for reporting and following a pregnancy was enhanced.

Section	Revision	Rationale
	or designee will inform the appropriate Sponsor representatives immediately but no later than 24 hours of when he or she becomes aware of it. The Investigator or designee will ensure that all relevant information is provided to the responsible Clinical Safety Group. All outcomes of pregnancy must be reported by the Investigator within 24 hours after he or she becomes aware of it. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed and documented even if the patient has discontinued the study. 7.13.2 Paternal Exposure Pregnancy of the patient's partner is not considered to be an AE; however, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed and documented, if possible. To capture information about a pregnancy from the partner of a male patient, the Investigator or designee must first obtain the consent of the male patient's partner. A consent form specific to this situation must be used. The outcome of any conception occurring from the date of the first dose of study drug until 30 days after the last dose should be followed and documented.	
8.1 Screening (Day −42 to Day −1)	Added the following statement: "Patients rolling from Group 1 to Group 2 do not require these assessments."	Clarification
8.2 Baseline Visit (Day 1)	Added the following statement: "Note: for patients rolling from Group 1 to Group 2, the Group 1 Week 12 assessments in Group 1 equal the baseline visit assessments in Group 2."	Clarification
8.14 through 8.20 Assessments performed at specific visits	These sections were updated or added to clarify what assessments are required for Group 2, Weeks 12–16, and for both groups at the end of treatment or early termination.	Revised to address inclusion of the 400-mg dose level
13.2 Schedule of Events for Group 2	Added this new table to clearly identify the assessments required for Group 2.	Revised to address inclusion of the 400-mg dose level