Title: Glucocorticoid Receptor Antagonism in the Treatment of Cushing Syndrome (GRACE): A Phase 3, Double-Blind, Placebo-Controlled, Randomized-Withdrawal Study of the Efficacy and Safety of Relacorilant

NCT Number: NCT03697109

Date: 17 May 2024

CLINICAL STUDY PROTOCOL CORT125134-455

Title	**Glucocorticoid Receptor Antagonism in the Treatment of Cushing Syndrome (GRACE): A Phase 3, Double-Blind, Placebo-Controlled, Randomized-Withdrawal Study of the Efficacy and Safety of Relacorilant**
IND Number	128625
EudraCT Number	2018-003096-35
Investigational Product	Relacorilant (CORT125134)
Medical Monitor	[redacted]
Sponsor	Corcept Therapeutics 149 Commonwealth Drive Menlo Park, California 94025 USA +1 (650) 327-3270
Version	Amendment 7
Date	17 May 2024

Good Clinical Practice Statement

This study will be conducted in compliance with the protocol, the International Council for Harmonisation Good Clinical Practice guidelines, and with the ethical principles contained in the Declaration of Helsinki (1989), or with the laws and regulations of the country in which the research is conducted, whichever provides greater protection of the human study participants. Compliance with these standards provides assurance that the rights, safety, and well-being of study participants are protected.

Confidentiality Statement

SPONSOR SIGNATURE PAGE

Protocol Title	Glucocorticoid Receptor Antagonism in the Treatment of Cushing Syndrome (GRACE): A Phase 3, Double-Blind, Placebo-Controlled, Randomized-Withdrawal Study of the Efficacy and Safety of Relacorilant
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APPROVAL STATEMENT

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

Signed and Dated:

[redacted]

[redacted]

PROTOCOL SYNOPSIS

Title	Glucocorticoid Receptor Antagonism in the Treatment of Cushing Syndrome (GRACE): A Phase 3, Double-Blind, Placebo-Controlled, Randomized-Withdrawal Study of the Efficacy and Safety of Relacorilant
Study Number	CORT125134-455
Name of Active Ingredient	Relacorilant
Name of Sponsor	Corcept Therapeutics
Phase	3
Study Centers	Approximately 60 sites (North America and other international sites)
Sample Size	Approximately 162 patients

Study Objectives

Primary

- To assess the efficacy of relacorilant for the treatment of endogenous Cushing syndrome based on blood pressure (BP) control at Week 12 of the Randomized-Withdrawal (RW) phase compared with placebo
- To assess the safety of relacorilant for the treatment of endogenous Cushing syndrome

Secondary

- To assess changes in cortisol excess-related comorbidities (including diabetes mellitus/ impaired glucose tolerance [DM/IGT] and body weight) in patients with endogenous Cushing syndrome treated with relacorilant over the RW phase

Study Population

This study includes patients with endogenous Cushing syndrome and associated DM/IGT and/or uncontrolled hypertension.

Number of Patients Planned

Approximately 162 patients are planned to enroll into a 6-month Open-Label (OL) phase of the study to ensure the randomization of approximately 46 patients with hypertension into the subsequent 3-month, placebo-controlled RW phase.

Duration of Patient Participation

Screening: Up to 6 weeks

Open-label treatment with relacorilant: 22–24 weeks

Randomized, double-blind, placebo-controlled, withdrawal phase: 12 weeks

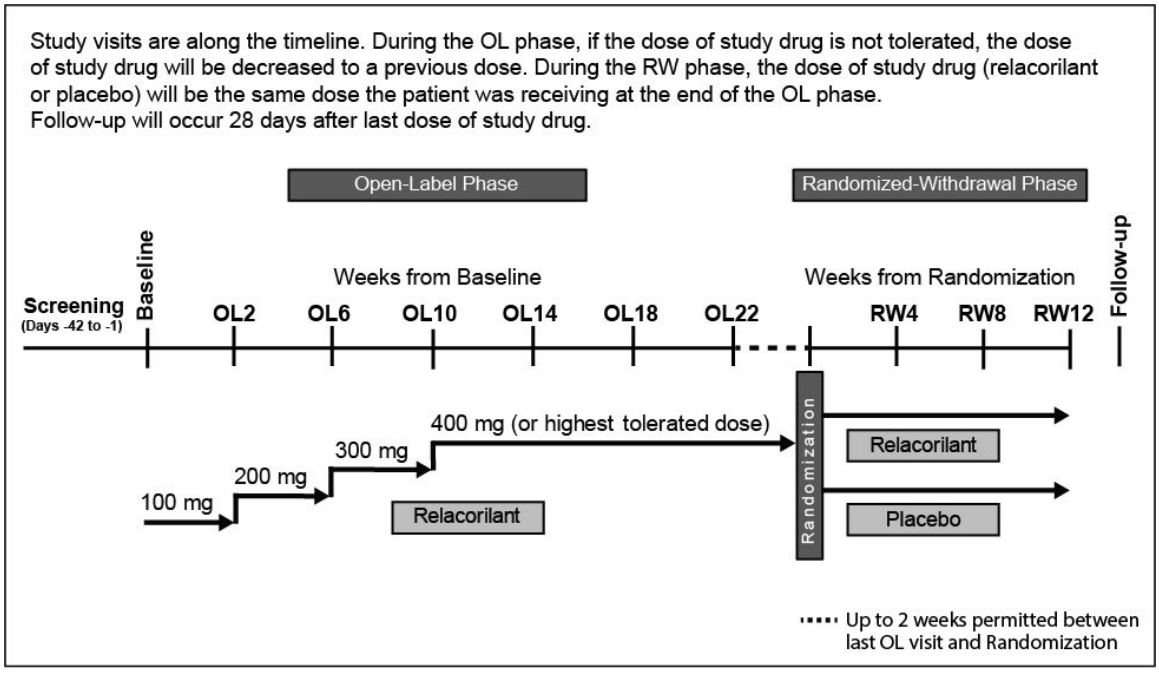
Follow-up: 4 weeks after the last dose of study drug

Total participation: Up to 46 weeks

Study Design

This is a Phase 3, double-blind, placebo-controlled, RW study to assess the efficacy, safety, and pharmacokinetics (PK) of relacorilant in patients with endogenous Cushing syndrome and concurrent DM/IGT and/or uncontrolled hypertension.

Figure S1 CORT125134-455 Study Design



Study Phases

The study phases are as follows.

Screening Phase

Up to 6 weeks to determine study eligibility.

Open-Label Phase (Baseline to Visit OL22)

Baseline is defined as Day 1 of the OL phase.

- The starting dose at Baseline will be 100 mg relacorilant once daily for 2 weeks
- From Visit OL2 through OL10, the dose of relacorilant will be increased every 4 weeks by 100 mg, as tolerated and based on improvement in signs and symptoms of Cushing syndrome, to a target dose of 400 mg once daily (i.e., to 200 mg at Visit OL2, to 300 mg at Visit OL6, and to 400 mg at Visit OL10). Clinical benefit in the Open-Label Phase will be assessed by the Investigator either by a change from Baseline or change from the previous visit considering the following factors:
  - BP measurements and anti-hypertensive medication
  - Glucose levels and diabetes medication
  - Body weight and waist circumference
  - Cushingoid appearance and striae
  - Sit-to-stand test
  - Beck Depression inventory
  - Cushing Quality-of-Life questionnaire
- If all symptoms of Cushing syndrome present at Baseline have resolved, no dose escalation will occur beyond that visit.
- Faster dose escalation during the open-label phase of the study for patients whose Cushing syndrome deteriorates may be allowed with medical monitor approval.
- If any planned dose escalation is postponed, Visit OL14 can be used for a final dose escalation

- Due to the COVID-19 pandemic, dose escalation up to 200 mg may occur remotely if necessary. Subsequent dose escalations, however, are permitted only after completion of safety assessments.
- Dose interruption, reduction, and re-escalation are permitted for safety/tolerability:
  - The relacorilant dose can be reduced to a previous dose if it is not tolerated
  - Re-escalation after a dose reduction is permitted until Visit OL18.

Randomized-Withdrawal Phase (Randomization to Visit RW12)

Patients who complete the OL phase and meet the following response criteria for DM/IGT or hypertension at Visit OL22 (see below and Section 3.6) will be randomized between Visit OL22 and up to 2 weeks after that visit in a 1:1 ratio to receive relacorilant or placebo for 12 weeks.

- **Patients with uncontrolled hypertension** at Baseline must meet one of the following response criteria:
  - ≥5 mm Hg decrease in mean systolic BP (SBP) and/or diastolic BP (DBP) from Baseline to Visit OL22, without worsening of either, based on 24-hour ambulatory BP monitoring (ABPM)

  Note: Increase of pre-existing blood pressure medication or initiation of new blood pressure medication, due to worsening in hypertension, disqualifies the patient from randomization into the RW phase. If a decrease in the BP medication occurred after the OL18 visit, reassess eligibility for randomization 4 weeks after the dose change.

- **Patients with DM/IGT** at Baseline must meet one of the following response criteria:

  In patients with DM
  - HbA1c has decreased by ≥0.5% from Baseline to Visit OL22
  - The 2-hour oGTT glucose is normalized (<140 mg/dL) or decreased by ≥50 mg/dL from Baseline to Visit OL22
  - Total daily insulin dose has decreased by ≥25% and HbA1c is unchanged or decreased compared with Baseline

  In patients with IGT
  - The 2-hour oGTT glucose is normalized (<140 mg/dL) from Baseline to Visit OL22

  Note: Increase of pre-existing diabetes medication or initiation of new diabetes medication, due to worsening of hyperglycemia, disqualifies the patient from randomization into the RW phase. If a decrease in the insulin dose happened after the OL18 visit, reassess eligibility for randomization 4 weeks after the dose change.

- **Patients with both DM/IGT and uncontrolled hypertension** at Baseline who do not meet the above-mentioned response criteria for both conditions must meet one of the following:
  - Meet one of the DM or IGT response criteria with no worsening in hypertension
  - Meet one of the uncontrolled hypertension response criteria with no worsening in DM or IGT

  Note: Increase of pre-existing diabetes or blood pressure medication or initiation of new diabetes or blood pressure medication due to worsening hyperglycemia or hypertension, disqualifies the patient from randomization into the RW phase. If a decrease in insulin dose or BP medication occurred after the Visit OL18, reassess eligibility for randomization 4 weeks after the dose change.

Treatment assignment and selected study assessments in the RW phase will remain blinded to the Investigators, the Sponsor, and the patients until after database lock.

No changes in the dose of study drug are allowed during the RW phase.

Rescue criteria during the RW Phase

2-hour oGTT and ABPM results during the RW Phase will be reviewed by an unblinded Medical Monitor to monitor patient safety. The unblinded Medical Monitor is unblinded to results of study assessments but is blinded to the treatment assignment.

- If a patient in the DM/IGT subgroup meets the first two of the following criteria, or if a patient in the hypertension subgroup meets the third criterion, the results will be communicated to the study site, and rescue medication may be initiated or increased as per Section 5.4.2.
  - Fasting glucose increases by 50 mg/dL from visit OL22, AND
  - 2-hour oGTT glucose increases by 100 mg/dL from Visit OL22
  - Increases in mean SBP or mean DBP by ABPM of more than 10 mm Hg from Visit OL22

Unblinding of the 2-hour oGTT or ABPM results will not result in the unblinding of study treatment.

In the event of rescue medication use before Visit RW12:

- In patients randomized to the DM/IGT subgroup, oGTT assessments will continue as planned until Visit RW12.
- In patients randomized to the hypertension subgroup, ABPM assessments will continue as planned until Visit RW12.

Patient Disposition

Patient Completion

- Patients who complete 12 weeks of the RW phase will return for the Follow-Up visit 28 days after the last dose of study drug. The Follow-Up visit will serve as the last study visit.
- Patients who complete 12 weeks of the RW phase, and entered an extension study within 28 days of the last dose of study drug, are not required to complete the Follow-Up visit. Visit RW12 will serve as the last study visit.

Early Termination

- Patients who complete the Visit OL22, but do not meet a response criterion for randomization, will be instructed to discontinue study drug. The Follow-Up visit will be conducted 28 days after the last dose of study drug and will serve as the last study visit.
- If a patient discontinues early from the OL phase, the patient will complete an Early Termination visit at the time of last dose of study drug (or soon thereafter). The Follow-Up visit will be conducted 28 days after the last dose of study drug and will serve as the last study visit.
- If a patient discontinues early from the RW phase, the patient will be instructed to return for Visit RW12 per the patient's original dosing schedule as well as the Follow-Up visit 28 days after the last dose of study drug. If RW12 is the return visit following early discontinuation from the RW phase, a 3-week visit window (2 weeks before the scheduled visit, 1 week after the scheduled visit) for RW12 is permitted.
- For patients who discontinue the study prior to the RW12 visit during the RW phase of the study and return for the RW12 visit, the follow up visit will be waived if the RW12 visit occurs at least 28 days after the last dose of administration of study drug.

Treatment Continuation

- Patients who complete the RW phase of the study will be permitted to continue relacorilant treatment in an extension study provided that they have at least 80% adherence with prescribed dosing (by capsule counts), AND are, in the opinion of the Investigator, expected to maintain clinical benefit from the study drug. Clinical benefit will be determined by the Investigator based on the changes during the Open-Label Phase in the following factors:
  - Hypertension
  - Hyperglycemia
  - Body weight and waist circumference
  - Clinical appearance
  - Sit-to-stand test
  - Psychiatric health and cognitive function
  - Cushing Quality-of-Life (QoL) score
- Patients who complete the OL phase of the study, but do not meet a response criterion for randomization, will be permitted to continue relacorilant treatment in an extension study if, in the opinion of the Investigator, they have benefitted from the study drug and are expected to maintain that benefit as noted above. The same adherence rule applies.
- Patients who continue on to the extension study within 28 days of last dose of study drug will not be required to complete the Follow-Up Visit. The last study visit for these patients will be either the Visit OL22 (if criterion for randomization is not met) or Visit RW12 (if the RW phase was completed).

Study Enrollment

Study enrollment will be monitored to ensure attainment of randomization targets. The number of patients enrolled in the OL phase may be adjusted to ensure a sufficient number of patients meeting response criteria to uncontrolled hypertension are randomized in the RW phase. Enrollment of patients may continue based on enrollment target projections.

Study Endpoints

Endpoints for both OL and RW phases are listed below. In the RW phase, (1) endpoints related to hypertension will be analyzed in those patients who met any response criterion for hypertension at Visit OL22; and (2) endpoints related to DM/IGT will be analyzed in those patients who met any response criterion for DM/IGT at Visit OL22.

Primary Endpoints

The primary efficacy endpoint will be assessed in the RW phase:

- **In patients with hypertension**, the proportion of patients with a loss of response with respect to hypertension from Visit OL22 to RW12 based on 24-hour ABPM as compared between relacorilant and placebo arms, where loss of response is defined as follows:
  - In patients who met only the SBP response criterion, an increase in SBP ≥5 mm Hg.
  - In patients who met only the DBP response criterion, an increase in DBP by ≥5 mm Hg.
  - In patients who met both the SBP and DPB response criteria, an increase in either SBP or DBP by ≥5 mm Hg.
  - Any increase or modification in antihypertensive medication due to worsening hypertension.
  - Patients discontinue treatment in RW phase for any reason.
- **In all patients**, assessment of safety based on treatment-emergent adverse events (TEAEs).

Secondary Efficacy Endpoints in the RW Phase

- Loss of response (AUC-based) in DM/IGT subgroup with response at OL22: proportion of patients with a loss of response with respect to hyperglycemic control from Visit OL22 to RW12, as compared between relacorilant and placebo arms, where loss of response is defined as a ≥10% increase from baseline in $AUC_{glucose}$ from Visit OL22 to RW12, use of rescue medication (initiation or increase in diabetes medication due to worsening of hyperglycemic control), treatment discontinuation for any reason in RW phase, or patients with missing RW12 $AUC_{glucose}$ values.
- Mean change from Visit OL22 to RW12 in 24-hour average SBP as compared between relacorilant and placebo.
- Mean change from Visit OL22 to RW12 in 24-hour average DBP as compared between relacorilant and placebo.
- Mean change from Visit OL22 to RW12 in body weight as compared between relacorilant and placebo.
- In patients with DM/IGT, the mean change in $AUC_{glucose}$ from Visit OL22 to RW12 as compared between relacorilant and placebo arms.
- In patients with DM/IGT, the mean change in HbA1c from Visit OL22 to Visit RW12, as compared between relacorilant and placebo.
- Comprehensive loss of response in DM/IGT subgroup with response at OL22: proportion of patients with a comprehensive loss of response with respect to hyperglycemic control from Visit OL22 to RW12, as compared between relacorilant and placebo arms, where the comprehensive loss of response is defined as follows:

  In patients with DM:

  - Use of rescue medication (initiation or increase in diabetes medication due to worsening of hyperglycemic control), treatment discontinuation for any reason in RW phase, or loss to follow-up,

  OR

  - HbA1c has increased by ≥0.3% at Visit RW12 (compared to OL22),

  OR

  - The 2-hour time point of the plasma 2-hours oGTT glucose test at Visit RW12 is abnormal (≥140 mg/dL) and has increased by at least 50% of the reduction observed between Baseline and Visit OL22.

  In patients with IGT:

  - Use of rescue medication (initiation or increase in diabetes medication due to worsening of hyperglycemic control), treatment discontinuation for any reason in RW phase, or loss to follow-up,

  OR

  - The 2-hour time point of the plasma 2-hour oGTT glucose test at Visit RW12 is abnormal (≥140 mg/dL) and has increased by at least 50% of the reduction observed between Baseline and Visit OL22.

Exploratory Efficacy Endpoints in the RW Phase

Continuous Endpoints

- Mean change from Visit OL22 to RW12 in 24-hour average heart rate (HR) as compared between relacorilant and placebo (based on ABPM).
- Mean SBP, DBP, and HR at RW12 (end of dosing interval) as compared between relacorilant and placebo (based on ABPM).
- Mean difference in daytime and nighttime average SBP, DBP, and HR (based on ABPM) at Visit RW12 as compared between relacorilant and placebo.
- Mean change from Visit OL22 to Visit RW12 in body fat composition measured with DXA scan as compared between relacorilant and placebo.
- Mean change from Visit OL22 to Visit RW12 in Cushing Quality-of-Life (QoL) score as compared between relacorilant and placebo.
- In patients with DM (HbA1c at Baseline ≥6.5%), the mean change from Visit OL22 to Visit RW12 in HbA1c, as compared between relacorilant and placebo.
- In patients with IGT at Baseline, the mean change from Visit OL22 to Visit RW12 in the 2-hour glucose value of the plasma 2-hours oGTT test as compared between relacorilant and placebo arms.
- The mean change from Visit OL22 to RW12 as compared between relacorilant and placebo in the following: waist circumference; lean mass measured by DXA; serum osteocalcin; the Beck Depression Inventory®-II (BDI-II) score; sit-to-stand test score; trail-making test score; sex-hormone levels (estradiol, total and free testosterone, sex-hormone–binding globulin, follicle-stimulating hormone, and luteinizing hormone); FKBP5 and other potential biomarkers of GR activity; urinary free cortisol (UFC), late-night salivary cortisol and plasma adrenocorticotropic hormone (ACTH); $AUC_{insulin}$, Matsuda Index, homeostatic model assessment of insulin resistance (HOMA IR), and daytime and nocturnal average blood pressure.
- In patients with adrenal CS, the mean change in the ACTH levels from Visit OL22 to RW12 as compared between relacorilant and placebo.

Endpoints Summarized with Proportions

- For patients in the hypertension subgroup, the proportion of patients with any increase or modification in antihypertensive medication due to worsening hypertension from Visit OL22 to Visit RW12 as compared between relacorilant and placebo.
- Proportion of patients who worsened, as assessed by the Global Clinical Response from Visit OL22 to Visit RW12 (i.e., a score of –1 at Visit RW12 as compared with Visit OL22).
- For patients in the DM/IGT subgroup, the proportion of patients with any increase in dose of diabetes medication from Visit OL22 to Visit RW12 as compared between relacorilant and placebo.
- For patients in the DM subgroup, the proportion of patients who achieve 25% reduction in $AUC_{glucose}$ from Baseline OL to Visit RW12 as compared between relacorilant and placebo.
- In all patients randomized in the RW phase, proportion of patients with a loss of response with respect to hypertension or hyperglycemia from Visit OL22 to Visit RW12 based on 24-hour ABPM and $AUC_{glucose}$ as compared between relacorilant and placebo arms, where loss of response is defined as follows:
  - In patients with hypertension only at Baseline OL:
    - In patients who met only the SBP response criterion, an increase in SBP ≥5 mm Hg.
    - In patients who met only the DBP response criterion, an increase in DBP by ≥5 mm Hg.
    - In patients who met both the SBP and DBP response criteria, an increase in either SBP or DBP by ≥5 mm Hg.

- Any increase or modification in antihypertensive medication due to worsening hypertension.
- Patients discontinue treatment in RW phase for any reason.

– In patients with DM/IGT only at Baseline OL:
- A ≥10% increase from Baseline RW in $AUC_{glucose.}$ from Visit OL22 to Visit RW12.
- Use of rescue medication (initiation or increase in diabetes medication due to worsening of hyperglycemic control).
- Treatment discontinuation for any reason in RW phase.
- Patients with missing RW12 $AUC_{glucose}$ values.

– In patients with hypertension and DM/IGT at Baseline OL, a loss of response will be defined as a loss of response with respect to either hypertension or hyperglycemic control (AUC-based) from Visit OL22 to Visit RW12, irrespective of which response criteria (hypertension or DM/IGT) they met to enter the RW phase.

Exploratory Efficacy Endpoints in the OL Phase

Continuous Endpoints

- In patients with uncontrolled hypertension, the mean change in SBP from Baseline to Visit OL22/ET.
- In patients with uncontrolled hypertension, the mean change in DBP from Baseline to Visit OL22/ET.
- Mean change in Cushing Quality-of-Life (QoL) score from Baseline to Visit OL22/ET.
- Mean change in body-fat composition from Baseline to Visit OL22/ET, as determined by DXA.
- Mean change in the Beck Depression Inventory®-II (BDI-II) score from Baseline to Visit OL22/ET.
- Mean change in body weight from Baseline to Visit OL22/ET.
- In patients with IGT, the mean change in 2-hour oGTT glucose from Baseline to Visit OL22/ET.
- In patients with DM (HbA1c ≥6.5% at Baseline), the mean change in HbA1c from Baseline to Visit OL22/ET.
- In patients with DM/IGT, the mean change in $AUC_{glucose}$ from Baseline to Visit OL22/ET.
- The mean change from Baseline to Visit OL22/ET in the following: waist circumference; lean mass measured by DXA; serum osteocalcin; the Beck Depression Inventory®-II (BDI-II) score; sit-to-stand test score; trail-making test score; sex-hormone levels (estradiol, total and free testosterone, sex-hormone–binding globulin, follicle-stimulating hormone, and luteinizing hormone); FKBP5 and other potential biomarkers of GR activity; urinary free cortisol (UFC), late-night salivary cortisol and plasma adrenocorticotropic hormone (ACTH); $AUC_{insulin}$, Matsuda Index, homeostatic model assessment of insulin resistance (HOMA IR), and daytime and nocturnal average blood pressure.
- In patients with adrenal Cushing syndrome (CS), the mean change in ACTH levels from Baseline to Visit OL22/ET.

Endpoints Summarized with Proportions

- In patients with hypertension, the proportion of patients who meet any of the hypertension response criteria at Visit OL22/ET.
- In patients with hypertension, the proportion of patients with reduction or discontinuation of antihypertensive medications from Baseline to Visit OL22/ET.
- The proportion of patients with a positive Global Clinical Response score at Visit OL22/ET.
- In patients with DM/IGT, the proportion of patients who meet any of the DM/IGT response criteria at Visit OL22/ET.

- In patients with IGT, the proportion of patients who achieved normalization of glucose based on the plasma 2-hours oGTT test and/or a reduction in the 2-hour glucose by 50 mg/dL from Baseline to Visit OL22/ET.
- In patients with DM (HbA1c ≥6.5% at Baseline), the proportion of patients with any decrease in dose of diabetes medication from Baseline to Visit OL22/ET.
- The proportion of patients meeting any DM/IGT or hypertension response criterion at Visit OL22/ET by dose at which response was first reached.
- In patients with DM/IGT, the proportion of patients with ≥25% decrease in $AUC_{glucose}$ from Baseline to Visit OL22/ET.
- In patients with DM/IGT, the proportion of patients with ≥0.5% decrease in HbA1c from Baseline to Visit OL22/ET.

Exploratory Pharmacokinetic Endpoints

- In patients with endogenous Cushing syndrome, the steady-state plasma exposures of relacorilant (additional details will be summarized in the PK Analysis Plan).

Inclusion Criteria

To enroll in the study, each patient must meet the following inclusion criteria:

1. Male or female, 18 to 80 years of age, inclusive.
2. Has a confirmed biochemical diagnosis of endogenous Cushing syndrome based on the presence of at least 2 of the following (Nieman et al. 2008):
   - UFC >upper limit of normal (ULN) in at least 2 complete 24-hour tests within the screening window
   - Late night salivary cortisol >ULN in at least 2 tests (using a salivette) within the screening window (Note: Test is not appropriate for night shift workers and cannot be used to evaluate eligibility)
   - 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 signing the informed consent.
3. Has at least 2 of the following clinical signs and symptoms of Cushing syndrome:
   - Bodily characteristics of a Cushingoid appearance (e.g., facial rubor, moon facies, dorsocervical fat pad, supraclavicular fat pad)
   - Increased body weight or central obesity
   - Proximal muscle weakness
   - Low bone mass based on DXA scan
   - Psychiatric symptoms (including depression or psychosis)
   - Skin manifestations: violaceous striae, acne, and/or hirsutism
   - Easy bruisability.
4. Has at least 1 of the following at Baseline:
   - DM (fasting plasma glucose ≥126 mg/dL and/or 2-hour oGTT plasma glucose ≥200 mg/dL at 2 hours or HbA1c ≥6.5%), or IGT (plasma glucose ≥140 mg/dL and <200 mg/dL on a 2-hour oGTT) (American Diabetes Association 2020)
   - Uncontrolled hypertension (mean SBP ≥135 to ≤170 mm Hg and/or mean DBP ≥85 to ≤110 mm Hg) based on 24-hour ABPM (Parati et al. 2014).
5. If receiving medical treatment for DM/IGT or hypertension, there has been no increase in medication dosage for at least 4 weeks prior to Baseline assessment.

6. If receiving medical treatment for depression, there has been no increase in medication dosage for at least 6 weeks prior to Baseline.
7. For women of childbearing potential, has a negative serum pregnancy test at Screening and negative urine pregnancy test at Baseline.

Exclusion Criteria

Patients who meet any of the following criteria will not be permitted entry to the study:

1. Has severe, uncontrolled hypertension (mean SBP >170 mm Hg or mean DBP >110 mm Hg at Screening), based on 24-hour ABPM.
2. Has poorly controlled DM (HbA1c >12% at Screening).
3. Has a known "long term" history of both hypertension and diabetes (defined as both hypertension and diabetes diagnosed >10 years prior to the initial diagnosis of endogenous CS).
4. Has a history of cyclic Cushing's syndrome with fluctuating clinical manifestations.
5. Has DM Type 1.
6. Has abnormal liver test results (total bilirubin >1.5×ULN or elevated alanine aminotransferase or aspartate aminotransferase >3×ULN at Baseline).
7. Has severe renal insufficiency (glomerular filtration rate ≤29 mL/min at Baseline).
8. Has uncontrolled, clinically significant hypothyroidism or hyperthyroidism.
9. Has prolonged QT interval corrected for heart rate using Fridericia's equation (QTcF) (>450 ms for men and >470 ms for women) with normal QRS interval (<120 ms) or QTcF interval >500 ms with wide QRS interval (≥120 ms).
10. Has received stereotactic radiation therapy for a Cushing syndrome-related tumor within 24 months of Baseline or conventional pituitary radiation therapy within 36 months of Baseline.
11. Has undergone pituitary surgery <3 months prior to Screening.
12. Has used or plans to use any of the following treatments for Cushing syndrome within 4 weeks prior to Baseline:
    - Mifepristone
    - Adrenostatic medications: metyrapone, osilodrostat, ketoconazole, fluconazole, aminoglutethimide, or etomidate
    - Serotonin antagonists: cyproheptadine, ketanserin, or ritanserin
    - Dopamine agonists: bromocriptine or cabergoline
    - Gamma-aminobutyric acid agonists: sodium valproate
    - Short-acting somatostatin analogs: octreotide, lanreotide, or pasireotide.
13. Has used or plans to use somatostatin receptor ligands: long-acting octreotide or pasireotide within 8 weeks prior to Baseline.
14. Patients who require inhaled glucocorticoid use and have no alternative option if their condition deteriorates during the study.
15. Has adrenocortical carcinoma.
16. Has used mitotane prior to Baseline.
17. Has ectopic Cushing syndrome and a life expectancy of <3 years or receiving chemotherapy.
18. Has pseudo-Cushing syndrome. Patients with known or suspected pseudo-Cushing 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 et al.1993, Giraldi et al. 2007, Yanovski et al. 1998) to rule-in or rule-out this possibility.

19. Has taken any investigational drug within 4 weeks prior to Baseline, or within less than 5 times the drug's half-life, whichever is longer.
20. Ongoing use of antidiabetic, antihypertensive, antidepressant or lipid-lowering medications that are highly dependent on CYP3A for clearance and that cannot undergo dose modification upon coadministration with strong CYP3A inhibitors.
21. Ongoing use of any strong CYP3A4 inducer or any other prohibited medications (Section 5.4.4).
22. Is pregnant or lactating.
23. Is a female patient 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) who cannot use a highly effective method of contraception (Section 4.6.2).
24. Has an acute or unstable medical problem that could be aggravated by treatment with the investigational study drug.
25. Has a history of hypersensitivity or severe reaction to the study drug, to a similar class of drug, or to the study drug's excipient.
26. In the Investigator's opinion, should not participate in the study or may not be capable of following the study schedule.
27. Has known HIV or hepatitis B or C infection.
28. Is a family member of one of the Sponsor's employees, the Investigator, or the site staff directly working on the study.
29. Has a history of unexplained vaginal bleeding or unexplained endometrial abnormalities.

Investigational Treatment, Dose, and Mode of Administration

The study drug will be administered orally and once daily, as capsules containing 100 mg of relacorilant (or matching placebo, as applicable).

The starting dose at Baseline will be 100 mg once daily for 2 weeks.

During dose escalation, all patients will be escalated in a stepwise manner from 100 mg to 400 mg once daily, based on tolerability and improvement in hypertension and/or hyperglycemia. The starting dose at Baseline will be 100 mg relacorilant once daily for 2 weeks, after which the dose will be increased to 200 mg. Then the dose will increase in 100 mg increments every 4 weeks. Dose escalation will be performed based on tolerability considering the following factors (only in patients whose current dose is well tolerated).

In patients with hypertension only, the mean 24-hour BP (based on ABPM):

- SBP is ≥130 mm Hg or
- SBP is <130 mm Hg and has not decreased by ≥5 mm Hg from Baseline.
- DBP is ≥80 mm Hg or
- DBP is <80 mm Hg and has not decreased by ≥5 mm Hg from Baseline.

In patients with DM/IGT only, the 2-hour glucose based on oGTT:

Note: For visit OL2, the fasting glucose assessment from the chemistry laboratory panel will be used for dose escalation purposes.

- is ≥140 mg/dL or fasting glucose is >100 mg/dL or
- is <140 mg/dL and has not decreased by ≥30 mg/dL from Baseline.

In patients with both DM/IGT and hypertension:

The mean 24-hour BP (based on ABPM):

- SBP is ≥130 mm Hg or
- SBP is <130 mm Hg and has not decreased by ≥5 mm Hg from Baseline.
- DBP is ≥80 mm Hg or
- DBP is <80 mm Hg and has not decreased by ≥5 mm Hg from Baseline.

AND

- is ≥140 mg/dL or fasting glucose is >100 mg/dL or
- is <140 mg/dL and has not decreased by ≥30 mg/dL from Baseline.
- Dose escalation may be held if the patient cannot safely tolerate escalation to the next dose.
- Faster dose escalation for patients whose Cushing syndrome deteriorates during the study may be allowed on a case-by-case basis after discussion and approval by the medical monitor.
- If any planned dose escalation is postponed, Visit OL14 can be used for a final dose escalation.
- If access of patients to the study site is restricted due to the COVID-19 pandemic, dose escalation up to 200 mg may occur remotely if necessary. Subsequent dose escalations, however, are permitted only after completion of safety assessments.
- Dose escalations start the day after the Visit at which they are approved by the Investigator.
- After normalization of hypertension and/or hyperglycemia, further dose escalation will be allowed considering the following factors:
  - Body weight and waist circumference
  - Cushingoid appearance and striae
  - Sit-to-stand test
  - Beck Depression inventory
  - Cushing Quality-of-Life questionnaire
- If all symptoms of Cushing syndrome present at Baseline have resolved, no dose escalation will occur beyond that visit.

Pharmacokinetics

Blood concentrations of relacorilant will be measured and PK examined in all patients at Visit OL18.

Statistical Methods

Analysis Populations

The ITT-RW population will include all patients who were randomized in the double-blind RW phase and received at least one dose of study drug. The mITT-RW population will include all patients in the ITT-RW population with at least one post-randomization efficacy assessment for primary efficacy endpoint (ABPM).

The per-protocol analysis population (PP-RW) will include all patients in the mITT-RW population who had no major protocol deviations that might impact the validity of the primary efficacy analysis. The ITT-RW population will be used for the analysis of the primary endpoint in the RW Phase. The mITT-RW and PP-RW populations will be used for supportive efficacy analyses of all endpoints in the RW Phase.

The ITT-OL population will include all enrolled patients who received at least one dose of study drug. The mITT-OL population will include all patients in the ITT-OL population with at least one post-baseline efficacy assessment for secondary efficacy endpoints. The per-protocol analysis (PP-OL) population will include all patients in the mITT-OL population who had no major protocol deviations that might impact the validity of the primary efficacy analysis. The ITT-OL, mITT-OL, and PP-OL populations will be used for supportive efficacy analyses of all endpoints in the OL Phase.

The safety population will consist of all enrolled patients who received at least 1 dose of study drug.

Statistical Analyses

All statistical hypotheses will be tested at a 2-sided 0.05 significance level, unless otherwise specified. No adjustments for multiplicity will be made for secondary and exploratory endpoints.

The primary efficacy endpoint will be assessed in the RW phase. The study will be considered to have a positive outcome if the primary endpoint reaches statistical significance.

Analysis of Primary Efficacy Endpoint

For the hypertension subgroup of the ITT-RW population, the primary analysis will be a responder analysis and the odds ratio for loss of response in hypertension control will be reported, as well as the percentage of patients with loss of response and 95% CI (using Clopper-Pearson method). The loss of response with respect to hypertension will be compared between treatment and placebo arms at Visit RW12 using a logistic regression model with 2 independent variables (treatment arm and stratification factor). In the hypertension subgroup, this stratification factor identifies patients with or without DM/IGT.

In the hypertension subgroup, loss of response in the RW phase is defined as: use of rescue medication for hypertension after randomization but before Visit RW12, discontinuation of treatment before Visit RW12, or increase in SBP/DBP of >5 mmHg documented after randomization.

This will be considered the primary analysis for the endpoint loss of response with respect to hypertension at Visit RW12 in the hypertension subgroup of the ITT-RW population.

Sensitivity analyses will be pre-specified in the SAP.

Analysis of Secondary Endpoints in the RW Phase

For continuous endpoints in the RW phase of the study the analysis will be performed using a linear MMRM model. Restricted maximum-likelihood (REML) estimation will be used. The MMRM model will include Visit OL22 value (for the respective endpoint) as a covariate; treatment, visit, treatment by visit interaction, and stratification factor as fixed effects; patients within treatment groups as random effects. An unstructured covariance structure will be used to model within-patient error, and the Kenward-Roger approximation will be used to model denominator degrees of freedom. This model is used after imputation of missing data at Visit RW12, using the retrieved drop-out approach. If fewer than 10 retrieved dropouts are available for the endpoint, then the main analysis will use a wash-out multiple imputation method instead of the retrieved dropout approach.

The analysis for each of the endpoints will determine whether there is a difference between treatment groups in terms of change from Randomization to Visit RW12. This will be accomplished by using appropriate linear contrasts of the parameters in the MMRM model described above. Additional details will be described in the SAP.

For all endpoints described as proportions in the RW phase, the point estimate and the 2-sided 95% CI will be calculated.

Sensitivity analyses will be pre-specified in the SAP.

Safety Analyses

TEAEs are defined as AEs that start or worsen after the first dose of study drug through 28 days after the last dose of study drug.

TEAEs will be displayed using the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term, as well as by severity and relationship to the study drug.

TEAEs will be summarized separately in the following four categories: Overall TEAEs, TEAEs that start prior to Randomization, TEAEs that start after randomization through the end of RW phase, TEAEs by treatment group, and TEAEs that start during the follow-up period by treatment group.

TEAEs for patients who were not randomized will be summarized separately. Serious AEs and TEAEs that lead to study-drug withdrawal or withdrawal from the study will be listed by patient.

Clinical laboratory test results (chemistry and hematology), vital sign measurements, and ECG interval results will be summarized as changes over the OL phase and RW phase by parameter and visit using descriptive statistics. Changes in the laboratory results during the follow-up period will be summarized separately.

Sample Size

Approximately 162 patients are planned to enroll into a 6-month OL phase of the study to ensure the randomization of approximately 46 patients with hypertension into the subsequent 3-month, placebo-controlled RW phase.

This calculation assumes that enrolled patients will consist of approximately 25% with DM/IGT only, 25% with hypertension only, and 50% with both DM/IGT and hypertension at Screening. Attainment of the randomization targets within the hypertension subgroup in the RW phase further assumes that 75% of patients that present with hypertension only randomize to the RW phase and 20% of patients that present with both comorbidities (DM/IGT and hypertension) respond to hypertension criteria at Visit OL22 and randomize to the RW phase. With these assumptions, a total of approximately 46 patients meeting response criteria will be randomized into the hypertension subgroup of the ITT-RW analysis population. Forty-six patients with hypertension (23 per treatment group) will ensure at least 90% power to detect the difference between placebo and treatment arms in loss of response (assuming a loss of response in 25% of patients in the treatment arm and 75% in the placebo arm). These calculations are based on a Fisher's exact test of proportions at the alpha=0.05 two-sided significance level.

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LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
ABPM	ambulatory blood pressure monitoring
ACTH	adrenocorticotropic hormone
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
$AUC_{0–24h}$	area under the concentration-versus-time curve from time 0 to 24 hours after dosing
$AUC_{glucose}$	area under the concentration-time curve for glucose
AUC_{inf}	area under plasma concentration-versus-time curve extrapolated to infinity
AUC_{last}	area under the concentration-versus-time curve at the last quantifiable time point
BDI-II	Beck Depression Inventory®-II
BP	blood pressure
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum plasma concentration
CT	computed tomography
CYP	cytochrome P450
DBP	diastolic blood pressure
DDI	drug-drug interaction
DHEA-S	dehydroepiandrosterone sulfate
DM/IGT	diabetes mellitus/impaired glucose tolerance
DRB	Data Review Board
DST	dexamethasone suppression test
DXA	dual energy X-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic case report form
ET	early termination
FDA	Food and Drug Administration
FKBP5	FK506-binding protein 5

Abbreviation	Definition
GCP	Good Clinical Practice
GR	glucocorticoid receptor
HbA1c	glycated hemoglobin
HOMA IR	homeostatic model assessment of insulin resistance
HPA	hypothalamic-pituitary-adrenal
HR	heart rate
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
mITT-RW	modified intent-to-treat–randomized withdrawal
MMRM	mixed model for repeated measures
MRI	magnetic resonance imaging
oGTT	oral glucose tolerance test
OL	open-label
PD	pharmacodynamic
PK	pharmacokinetics
PPG	postprandial glucose
PR	progesterone receptor
QoL	quality-of-life
QTc	corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's equation
REML	restricted maximum likelihood
RW	randomized withdrawal

Abbreviation	Definition
s	serum
SAE	serious adverse event
SBP	systolic blood pressure
$t_{1/2}$	half-life
T3	triiodothyronine
T4	thyroxine
TEAE	treatment-emergent adverse event
u	urine
UFC	urinary free cortisol
ULN	upper limit of normal
US	United States

1 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 Therapeutic Area

Endogenous Cushing syndrome is a rare multisystem disorder that results from overproduction of the glucocorticoid hormone cortisol. In both adults and children, Cushing syndrome is most commonly caused by an adrenocorticotropic hormone (ACTH)-secreting pituitary tumor (Cushing disease). Other forms of Cushing 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 cause of the excess cortisol. Depending on the nature of the underlying tumor (i.e., benign versus malignant, localized versus metastatic), the selected treatment may be surgery, radiotherapy, medical therapy, or a combination of these.

Pharmacological treatment serves to control the disease after unsuccessful surgery or recurrence (Nieman et al. 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 four United States (US) Food and Drug Administration (FDA)-approved medical therapies for endogenous Cushing syndrome. The first, mifepristone (Korlym®), was approved for the control of diabetes mellitus/impaired glucose tolerance (DM/IGT) secondary to hypercortisolism in adult patients with endogenous Cushing syndrome who have DM/IGT and have failed surgery or are not candidates for surgery. The second, pasireotide (Signifor®), is a somatostatin receptor agonist approved for the treatment of adult patients with Cushing disease for whom pituitary surgery is not an option or has not been curative. The third, osilodrostat (Isturisa®) is a cortisol-synthesis inhibitor approved for the treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative. The fourth, levoketoconazole (Recorlev®), is a cortisol synthesis inhibitor indicated for the treatment of endogenous hypercortisolemia in adult patients with Cushing syndrome for whom surgery is not an option or has not been curative.

Relacorilant (CORT125134) is a potent, selective glucocorticoid receptor (GR) antagonist being developed for the treatment of Cushing syndrome. Relacorilant is a high-affinity antagonist of the GR (inhibition constant <1 nM in a human GR binding assay and <10 nM in a human functional assay). Although the mechanism of action of relacorilant is similar to that of mifepristone, relacorilant does not bind to the progesterone receptor (PR). Given its selective and potent GR antagonism, relacorilant has the potential advantage compared with mifepristone of not having any antiprogesterone effects, including endometrial hypertrophy and the potential for irregular vaginal bleeding.

1.2 Clinical Summary

A brief summary of relacorilant clinical studies is presented. Further details on the studies, design, and results are presented in the Investigator's Brochure.

In the first study of relacorilant, a Phase 1 single-ascending dose/multiple-ascending dose study (Study CORT125134-120; NCT03508635), 84 healthy subjects received single doses of up to 500 mg or repeated doses of up to 250 mg daily ("clinical-pharmacology" formulation, an earlier formulation with a higher bioavailability than the current "clinical-trial formulation"). Pharmacodynamic data were generated following administration of prednisone alone and in combination with relacorilant. Single doses of 500 mg of relacorilant or multiple doses of 250 mg daily prevented changes in lymphocytes, eosinophils, and osteocalcin induced by prednisone alone, as well as changes in the mRNA expression of glucocorticoid-regulated genes (FK506 binding protein 5 [FKBP5]). During the repeated-dose parts of Study CORT125134-120, there was a dose-related trend in subjects who reported at least 1 treatment-emergent adverse event (TEAE): 44.4% (50 mg), 66.7% (150 mg), and 85.7% (250 mg), compared with 50% of placebo-treated subjects. The most commonly reported TEAEs were within the system organ class musculoskeletal and connective tissue disorders. At a relacorilant dose of 500 mg once daily, 77.8% of subjects of in the 500 mg group reported at least one moderate or severe TEAE, compared with <22.5% in the groups receiving placebo and lower relacorilant doses. This 500 mg dose level (with the higher bioavailability formulation) was terminated prematurely due to lack of tolerability. No serious AEs were reported in this group.

A Phase 1 multiple-ascending-dose study was conducted to characterize the steady-state PK of and determine the exposure range of the clinical-trial formulation following administration of daily doses of 150 mg, 250 mg, or 350 mg for 14 consecutive days in healthy subjects (n=32) (Study CORT125134-453). Consistent with historical data, relacorilant exposure increased in a time-dependent and greater than dose-proportional manner. All subjects achieved steady-state conditions by Day 14, and all subjects had a steady-state exposure (Day 14 area under the concentration-time curve from 0 to 24 hours postdose, $AUC_{0\text{-}24h}$) that was less than the 40 µg•h/mL exposure limit guided by results of the toxicology studies. Relacorilant was well tolerated in all subjects at all dose levels. No serious or severe TEAEs have been reported. One subject receiving relacorilant 250 mg withdrew consent and discontinued the study due to a related TEAE of moderate dyspepsia. Additionally, the PK data from Study CORT125134-453 indicate that the relacorilant exposure in healthy subjects is similar to that observed in patients with endogenous Cushing syndrome at the same dose level in Study CORT125134-451.

A Phase 1 human absorption, distribution, metabolism, and excretion (ADME) study was conducted in healthy subjects to assess the mass balance recovery, pharmacokinetics (PK), metabolite profile and elimination of relacorilant. The major components in human plasma were CORT125336 (both diastereoisomers), metabolite m/z411, CORT125337 (first diastereoisomer), parent relacorilant, and metabolite CORT125295. Relacorilant represented 38% of the circulating radioactivity based on maximum plasma concentration (C_{max}) and 6.2% based on AUC at the last quantifiable time point (AUC_{last}) and suggests rapid metabolism of relacorilant. The mean half-life ($t_{1/2}$) of relacorilant was 23.1 hours. A single dose of [^{14}C]-relacorilant was well tolerated, no severe or serious TEAEs were reported, and no subject was withdrawn as a result of a TEAE. The mass balance recovery of total radioactivity did not differ between male and female subjects.

The effect of food on a single dose of relacorilant (350 mg) was evaluated clinically (Study CORT125134-123; NCT03442621) in healthy subjects following administration of relacorilant (clinical-trial formulation) with a high-fat meal or with a standard, moderate -fat meal, relative to

fasting conditions. The exposure (AUC) of relacorilant increased approximately 2-fold on administration under fed conditions, relative to fasting conditions. The increase in relacorilant exposure was similar with both meal types. A serious adverse event (SAE; pulmonary embolism) occurred in 1 subject 20 days after receiving the last dose of relacorilant.

The potential effect of relacorilant as a perpetrator of cytochrome P450 (CYP)-mediated drug-drug interactions (DDI) was evaluated clinically (Study CORT125134-126; NCT03457597). Healthy subjects received single oral doses of the probe substrates midazolam (CYP3A), metoprolol (CYP2D6), pioglitazone (CYP2C8), tolbutamide (CYP2C9), and omeprazole (CYP219) in the presence or absence of steady-state concentrations of relacorilant (350 mg once-daily; clinical-trial formulation). Following single-dose administration of probe substrates of CYP activity in the presence of steady-state concentrations of relacorilant, no relevant effect of relacorilant was observed on CYP2D6, CYP2C8, CYP2C9, CYP2C19, However, relacorilant was shown to be a strong CYP3A inhibitor, resulting in midazolam AUC extrapolated to infinity (AUC_{inf}) and C_{max} of 8.8-fold and 3.3-fold higher, respectively, relative to midazolam alone; additional guidance is provided in Section 5.4.4. One subject discontinued due to an AE of pancreatitis, acute, Grade 3 (severe), not serious, not related to either relacorilant or probe substrates. No other treatment-related adverse events (TEAEs) led to withdrawal of study drug, study-drug interruption, or reduction of dose.

The effect of a strong inhibitor of CYP3A on a single dose of relacorilant was evaluated in healthy subjects (Study CORT125134-124; NCT03512548, Part 1). Following coadministration of a single dose of relacorilant (350 mg; clinical-trial formulation) with itraconazole (200 mg), relacorilant AUC_{inf} and C_{max} were 3.5-fold and 2.0-fold higher, respectively, versus relacorilant alone. No TEAEs were reported that led to withdrawal of study drug, study-drug interruption, or reduction of dose. Further evaluation is ongoing to determine the potential effect of a strong CYP3A inhibitor on steady-state concentrations of relacorilant. Because relacorilant is a strong CYP3A inhibitor as well as a CYP3A substrate, it undergoes autoinhibition, and the addition of another strong CYP3A inhibitor is not expected to result in a substantial DDI.

Study CORT125134-451 (Study of the Safety and Efficacy of CORT125134 in the Treatment of Endogenous Cushing's Syndrome; NCT02804750) is a Phase 2, open-label, multicenter, dose-escalation study in patients with endogenous Cushing syndrome. The study is ongoing, dosing has completed, CSR is under preparation. Group 1 (n=17) had a two-step dose escalation (monthly) of once-daily relacorilant (dose range, 100–200 mg, clinical-trial formulation; total treatment period, 12 weeks), and Group 2 (n=18) had a three-step dose escalation (monthly) of once-daily relacorilant (dose range, 250–400 mg, clinical-trial formulation; total treatment period, 16 weeks).

Applying the response criteria selected for this Phase 3 study (Section 3.1.3.1) to the data from Study 451, among patients with hyperglycemia, 15% of patients in Group 1 and 50% percent of patients in Group 2 responded. Among patients with hypertension, 41.7% of patients in Group 1 and 63.7% of patients in Group 2 responded.

Of the 17 patients enrolled in Group 1, all but 1 patient completed the study. A total of 101 TEAEs were reported, with 88.2% of patients reporting at least one. The majority of patients (70.6%) experienced events that were considered related to relacorilant. The most common TEAEs in Group 1 were back pain, pain in extremity, diarrhea, and headache, each with 23.5%

of patients experiencing each of these TEAEs at some point in the study. Most of the events were mild or moderate, and none were serious. One patient discontinued study at 6 weeks due to worsening hypertension that was not attributed to relacorilant. Study drug was withdrawn for the subject who discontinued.

Of the 18 patients enrolled in Group 2, 8 (44.4%) completed the study, 13 patients (72.2%) completed Week 12. In Group 2, 228 TEAEs were reported, with all patients reporting at least one TEAE. The majority of patients (83.3%) experienced events considered related to relacorilant. The most common TEAEs in Group 2 were back pain (38.9%), nausea and headache (27.8%), and arthralgia, dizziness, myalgia, abdominal pain, pain in extremity, dyspepsia (22.2% each).

Eight patients in Group 2 had TEAEs that led to study-drug discontinuation, including 3 patients with TESAEs and 5 patients with nonserious TEAEs (musculoskeletal AEs for 3 patients and peripheral neuropathy and abnormal glucocorticoids for 1 patient each). All events that led to study-drug discontinuation in Group 2 were considered related to study drug with the exception of one TEAE of neck pain. The musculoskeletal TEAEs improved with dose decreases, but returned on dose re-escalation. In those patients, decrease of the dose of relacorilant improved the adverse events.

For the entire study, five TESAEs were reported in 4 patients. All TESAEs were Grade 3 in severity. Three patients (8.57%) had TESAEs (polyneuropathy, myopathy, and acute myocardial infarction) that were considered related to study drug and led to study-drug discontinuation.

Relacorilant exposure in patients with endogenous Cushing syndrome (Study CORT125134-451) remained well below the 40 µg·h/mL cap (exposure limit guided by results of the toxicology studies) at doses up to 400 mg.

1.3 Rationale for Study Design and Dose Regimen

1.3.1 Rationale for Study Design

The activity of relacorilant has been demonstrated in various in vitro assays, and relacorilant was shown to be well tolerated in several clinical studies. The combination of the preclinical and clinical findings supports the continued evaluation of relacorilant in patients with Cushing syndrome.

The study design includes an open-label (OL) phase, followed by a 12-week, randomized, double-blind, placebo-controlled withdrawal phase. Only patients meeting response criteria at the end of the OL phase will be eligible for the randomized-withdrawal (RW) phase. An RW design provides predictive enrichment for the comparison of active treatment to placebo.

The OL phase for the determination of responders (i.e., the population to be randomized) has two precedents: First, mifepristone, another GR antagonist, was approved following an OL study that demonstrated clinical improvement in glucose control of individual patients, using each patient as his or her own control. Second, the Phase 2 study of relacorilant (Study CORT125134-451) demonstrated clinical improvement in glucose control as well as in hypertension.

The use of an OL phase followed by a placebo-controlled randomized withdrawal phase has been used in two clinical trials in this indication (i.e., studies of levoketoconazole and LCI699).

Patients randomized to placebo are expected to experience a gradual loss of response during the 12-week RW phase, and to return toward their baseline status. Increases in antidiabetic or antihypertensive medications are allowed during the RW phase if needed (Section 5.4.2).

This study will evaluate the efficacy and safety of GR antagonism by relacorilant, with an emphasis on blood pressure (BP) control, in patients with endogenous Cushing syndrome. To examine the many manifestations of Cushing syndrome in the study patients, several other efficacy assessments will be used to assess clinical benefit, including the use of antidiabetic and/or antihypertensive medications, glycated hemoglobin (HbA1c), and body-fat composition. Clinical benefit will also be assessed according to the exploratory efficacy endpoints detailed in Section 3.6.

This design of this study accounts for relevant US FDA regulatory guidance and will be conducted in compliance with the protocol, Good Clinical Practice (GCP) guidelines, and the applicable regulatory requirements.

1.3.2 Rationale for Dose Selection and Regimen

Dose selection for this study was based on PK and safety results from Phase 1 studies in healthy subjects (CORT125134-120, CORT125134-123, and CORT125134-453) and safety, efficacy, and PK results in a Phase 2 study in patients with Cushing syndrome (CORT125134-451).

Across all of these studies, exposure to relacorilant (as $AUC_{0\text{-}24h}$) at steady-state was well below 40 µg·h/mL and was consistent between healthy subjects and patients with Cushing syndrome. The PK of relacorilant support daily dosing.

In the Phase 2, open-label, multicenter Study CORT125134-451, 35 patients with endogenous Cushing syndrome received relacorilant in escalating doses ranging from 100 mg/day to 200 mg/day (Group 1, 12 weeks) and ranging from 250 mg/day to 400 mg/day (Group 2, 16 weeks). Preliminary results indicate that treatment with relacorilant in patients with endogenous Cushing syndrome results in improved glycemic and hypertension control.

In Group 1, clinically significant changes in DM/IGT and hypertension control were generally observed starting with the 200-mg dose, which was well tolerated. In Group 2, a higher proportion of patients responded based on the Phase 3 response criteria (Section 1.2), but also a higher proportion experienced TEAEs (especially musculoskeletal complaints) and/or discontinued study.

The Phase 2 data suggest that most responders will achieve clinical benefit along with good tolerability at a relacorilant dose of 200 mg or 300 mg daily, but that some patients (analogous to experience with the predecessor drug, mifepristone), will require higher doses. Based on these safety, efficacy, and PK considerations, the dose range for the examination of both safety and efficacy in the protocol is 200–400 mg, the dose range already tested in the Phase 2 study.

The Phase 2 experience suggests that patients may best tolerate a gradual dose escalation. The exposures in the patients with Cushing syndrome receiving 200 mg (in Group 1) and patients receiving 250 mg were similar. However, patients in Group 2, who started dosing with 250 mg relacorilant, experienced TEAEs (especially musculoskeletal symptoms) at a higher frequency and with greater intensity compared with patients who received 200 mg after a slow titration starting from 100 mg daily. Therefore, to maximize treatment persistence, patients in this

Phase 3 study will start at 100 mg daily for the first 2 weeks of dosing before escalating to 200 mg daily and continuing with subsequent dose escalations to a target dose of 400 mg once daily, as tolerated.

1.4 Rationale for Selection of Primary Endpoint

Due to the mechanism of action of relacorilant (a GR antagonist), cortisol levels cannot be used as a primary endpoint as they are in studies of steroidogenesis or ACTH secretion inhibitors. Therefore, clinical endpoints must be used, as in the case of the marketed drug, mifepristone (Korlym®). The primary indicator of clinical response in this protocol is improvement in hypertension, which is a very common manifestation of Cushing syndrome and for which there are robust, objective measures. In this protocol, the response criteria for BP control and for blood glucose control determine the selection of patients who will enter the placebo-controlled portion of the study.

For hypertension control, the protocol employs 24-hour ambulatory blood pressure monitoring (ABPM), the gold-standard measurement. For this test, a decrease of 5 mm Hg in either systolic or diastolic BP is clinically significant, and this is the BP response criterion. Unlike the predecessor drug, mifepristone, relacorilant has not caused significant increases in cortisol levels in Phase 2 patients with Cushing syndrome. Therefore, relacorilant does not pose any concern that improvement in BP due to general improvement in Cushing syndrome could be offset by cortisol stimulation of the mineralocorticoid receptor (which increases BP). Thus, the improvements in hypertension seen in the Phase 2 study are expected to be confirmed in this Phase 3 study.

For the RW phase, the criterion for loss of response in regards to HTN control is the same (but reverse) as for response in the OL phase of the study—an increase of 5 mm Hg or greater. For blood pressure, a responder analysis is preferred due to absence of a single parameter that incorporates both systolic BP (SBP) and diastolic BP (DBP).

1.5 Rationale for Selection Criteria for Patients Eligible in the Randomized Withdrawal Phase

Selection of patients eligible for randomization in the RW phase is based on the improvement of common comorbidities observed in patients with Cushing syndrome, hypertension, or hyperglycemia. Hypertension response criteria are described in Section 1.4.

For glucose control, the evaluation of clinical benefit depends on the circumstances at Baseline. The response criteria in this protocol are based on 1) decreases in HbA1c, 2) decreases in the 2-hour glucose level in the oral glucose tolerance test (oGTT), and 3) reduction in diabetes medication and are intended to encompass the range of clinically significant improvements seen in patients experiencing better control of their hyperglycemia.

For any patient with hyperglycemia, a reduction in HbA1c of ≥0.5% is clinically significant (Prandin 2017; Starlix 2018; Gerich 2013; Esposito et al. 2004; EMA/CHMP 2014; Castinetti et al. 2014). For patients with lesser degrees of hyperglycemia, improvements may not be reflected in changes in HbA1c (which is less sensitive below a starting point of 6.5%), but will be evident from the oGTT. The 2-hour oGTT glucose level has been used as an endpoint in several trials with diabetes drugs (Prandin 2017; Starlix 2018; Gerich 2013; Esposito et al. 2004). In these

studies, a change in the 2-hour postprandial glucose (PPG) by 50 mg/dL was associated with a clinically meaningful improvement in the HbA1c, and this change is regarded by diabetologists as clinically meaningful. Finally, a substantial reduction in diabetes medication—a 25% reduction in total daily insulin dose triggered by the treating physician either to prevent hypoglycemia after observing significant fasting or postprandial glucose reductions or after observing hypoglycemic values in a patient to prevent future hypoglycemic episodes without worsening of the HbA1c represents a significant clinical benefit.

1.6 Benefits and Risks

Glucocorticoid receptor antagonism is a proven mechanism of action for the treatment of the DM/IGT secondary to hypercortisolism in adult patients with Cushing syndrome (Fleseriu et al. 2012). Because the mechanism of action of relacorilant is similar to that of mifepristone, with the exception that it does not bind the PR, relacorilant is expected to effectively treat Cushing syndrome, but without the drawbacks of progesterone receptor antagonism that may result in untoward reproductive effects and/or interruption of therapy.

In the Phase 2 study (Study CORT125134-451) in patients with endogenous Cushing syndrome, relacorilant showed evidence of clinical benefit based on improvement of cortisol-excess–related comorbidities. The drug was generally well tolerated, with the upper bound on dosing being typically musculoskeletal complaints, a tolerability issue that patients can report.

Compared with the predecessor drug mifepristone, relacorilant offers two key safety advantages: lack of affinity for the PR, and lack of significant cortisol rise (a driver of hypokalemia in the marketed GR antagonist mifepristone).

Based on the mechanism of action of relacorilant, there is a theoretical risk of excessive GR antagonism, which could manifest by weakness, tiredness, dizziness, hypoglycemia, dehydration, weight loss, nausea, vomiting, diarrhea, and muscle aches. Since relacorilant does not affect the mineralocorticoid receptor, it is unlikely that hypotension would occur in the absence of antihypertensive medication. Because plasma glucocorticoid levels are not decreased with relacorilant administration, a biochemical diagnosis of excessive GR antagonism is not possible; diagnosis must rely on clinical assessment. In cases of suspected excess GR antagonism, study drug will be interrupted for 3 days and supplemental glucocorticoid will be given in high doses to overcome the GR antagonism (Table 2).

The safety profile of relacorilant in study patients will be monitored by AEs, physical examinations, measurement of vital signs, 12-lead electrocardiograms (ECGs), and blood tests for analysis of clinical chemistry and hematology parameters.

Patients meeting response criteria will be randomized 1:1 to continue relacorilant or receive a placebo equivalent (i.e., have relacorilant withdrawn). Patients proceeding into the RW phase will be at risk for relapse of symptoms of Cushing syndrome, including worsening of diabetes, hypertension, and weight gain.

In vitro data indicate that relacorilant is metabolized by multiple CYP enzymes (CYP3A4, CYP2C8, and CYP3A5) and by carbonyl reductases. Data also indicate the potential for relacorilant to perpetuate drug-drug interactions via inhibition of CYP3A and transporter pathways. Patients taking any prohibited medication are excluded from this study (refer to

Section 5.4). If a concomitant medication is required to treat an AE, in selecting the appropriate concomitant medication, the Investigator must consider the risk of drug-drug interaction. The Medical Monitor must approve all concomitant medications required to treat an AE if there is a potential for drug-drug interaction. If necessary, the patient will be withdrawn from the study.

Study procedures include venous blood sampling and noninvasive procedures, including ECG recording, imaging, and vital-sign measurement. During cannulation, more than 1 attempt may be needed to insert the cannula in a vein of a patient, and it is possible that bruising and/or inflammation may be experienced at the site of cannulation. The total volume of blood collected will not exceed 850 mL unless the Investigator or designee considers additional unplanned collection(s) are required for safety laboratory tests.

More information on the risks and benefits of relacorilant is provided in the Investigator's Brochure.

1.6.1 Study Conduct during COVID-19 Pandemic

The United States (US) Food and Drug Administration (FDA), as well as the European Medicines Agency (EMA), acknowledge the impact of COVID-19 on the health system and broader society, and recognize the impact it could have on trials and trial participants (FDA 2020, EMA 2020). Both agencies underscore that safety of trial participants is paramount.

In addition to the risks/potential benefits to trial participation, the added challenges of conducting a clinical trial during the time of the public health emergency related to COVID-19 require the Sponsor to perform initial and ongoing risk assessment to determine its potential impact on the safety and confidentiality/privacy of the trial participant, integrity of the trial, and the benefit of the trial for participants and society.

With regard to Protocol CORT125134-455, Corcept has been working with clinical investigators and Institutional Review Boards (IRBs)/Ethics Committees (ECs) on a continuing basis to ensure that the patient's safety, welfare, and rights are best served by participating in this trial. Corcept will continue to communicate guidance and provide support to clinical study sites during the COVID-19 pandemic.

- Corcept recognizes that the protocol may require modification to ensure integrity of the trial and appropriate safety monitoring are implemented for all enrolled participants. This may involve alternative methods for safety and study assessments (i.e., phone contact, virtual study visits, use of alternative locations for assessment, including local labs or imaging centers, etc.). New processes or modification of protocol-described processes may be required, depending on the specific situation.
- Corcept also recognizes that, depending on the specific situation, treatment with the investigational product may be ended or paused.
- Lastly, Corcept recognizes that if the study cannot be properly conducted under the existing protocol, it could be necessary to amend the protocol, stop recruitment, and/or withdraw trial participants.

All decisions will be properly documented. Risk assessment will be made on an ongoing basis.

As required, information pertaining to protocol modifications (including study visits, remote study monitoring, investigational drug supply distribution, etc.) as a result of COVID-19 will be

recorded and submitted to Regulatory Agencies and/or IRBs/ECs in accordance with COVID-19 guidances issued at country level and/or by IRB/EC, unless otherwise requested/required by these entities.

As described in the EMA guideline, "It is expected that the sponsor performs a risk assessment of each individual ongoing trial and the investigator of each individual trial participant and implement measures, which prioritise trial participant safety and data validity. **In case these two conflict, trial participant safety always prevails.**"

The following risk assessments and aspects of trial conduct will be considered by Corcept on an ongoing basis in conjunction with clinical investigators and IRBs/IECs, as applicable, to ensure that the safety of trial participants can be maintained:

- Whether the limitations imposed by the COVID-19 public health emergency on protocol implementation pose new safety risks to trial participants, and whether it is feasible to mitigate these risks by amending study processes and/or procedures.
- Whether there will be continued availability of the clinical investigator/sub-investigators to provide oversight of the trial, and properly assess and manage safety issues that may emerge.
- Whether there will be sufficient trial support staff given the evolving COVID-19 situation, and that staff are appropriately trained and could be available to handle the expected tasks, and that they have adequate equipment and materials.
- Whether clinical investigator sites will remain open to trial participants for required in person assessments or whether the clinical investigator has the ability to provide required in-person assessments at an acceptable alternate location(s), or whether such protocol-specified in-person assessments can instead be conducted virtually.
- Whether there is continued supply of the investigational product and/or trial supplies essential to maintaining appropriate safety monitoring or other key trial procedures for trial participants.
- Whether there is continued availability of, and support for, information technology systems and any other technological tools needed to support the trial.
- Whether there will be continued operations of, and adequate communications with, IRB/EC, if applicable, to support trial needs.
- Whether it is feasible to conduct the trial in light of any COVID-19 public health measures implemented by Federal/Government, state, and/or local authorities to control the virus.

Depending on the specific situation, additional assessments may be added. Study participants will be informed of changes to the study and monitoring plans that could affect them. Processes for remote monitoring will include the protection of trial participant data privacy and confidentiality. Study participants may choose not to participate in this study or may leave this study at any time, without having to give a reason. Study participants will still receive care for their condition and will not be penalized or lose any benefits to which they are otherwise entitled. They will not lose any rights they are entitled to as a study participant.

Patients with endogenous Cushing syndrome are immunocompromised due to a direct suppressive effect of high cortisol on the bone marrow and immune cells, as well as due to an effect on the immune system of the cortisol-excess–related comorbidities (e.g., diabetes,

hypertension, obesity). Patients with Cushing syndrome who remain untreated are at high risk for infections from common and uncommon pathogens. Infection is the second most common cause of death among patients with overt Cushing syndrome (Dekkers et al. 2013) and in patients with milder forms of hypercortisolism due to cortisol-secreting adrenal adenomas (Debono et al. 2014). In Study CORT125134-451, in which patients with endogenous Cushing syndrome were treated with relacorilant, in the high-dose group, we observed an overall increase in the number of lymphocytes (which is often suppressed in this patient population).

In addition, should a patient in the study become infected with COVID-19, the Investigator should consult the Medical Monitor regarding any possible interactions of relacorilant with the various treatment options.

2 STUDY OBJECTIVES

2.1 Primary Objectives

- To assess the efficacy of relacorilant for the treatment of endogenous Cushing syndrome based on BP control at Week 12 of the Randomized-Withdrawal (RW) phase compared with placebo
- To assess the safety of relacorilant for the treatment of endogenous Cushing syndrome

2.2 Secondary Objective

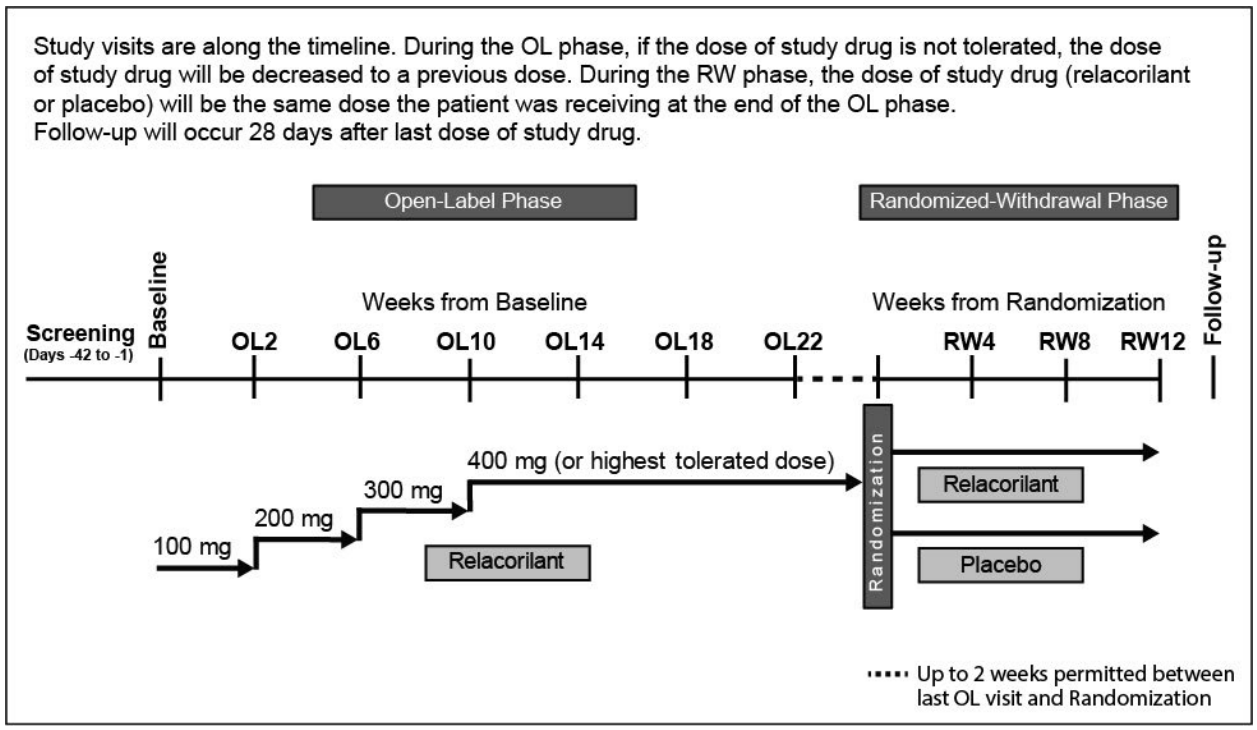
- To assess changes in cortisol excess-related comorbidities (including DM/IGT, and body weight) in patients with endogenous Cushing syndrome treated with relacorilant over the RW phase

3 STUDY DESIGN

3.1 Overall Design

This is a Phase 3, double-blind, placebo-controlled, RW study to assess the efficacy, safety, and PK of relacorilant in patients with endogenous Cushing syndrome and concurrent DM/IGT and/or uncontrolled hypertension (Figure 1).

Figure 1 CORT125134-455 Study Design



The study phases are as follows:

3.1.1 Screening Phase

Up to 6 weeks to determine study eligibility.

3.1.2 Open-Label Phase (Baseline to Visit OL22)

Baseline is defined as Day 1 of the OL phase.

- The starting dose at Baseline will be 100 mg relacorilant once daily for 2 weeks.
- From Visit OL2 through Visit OL10, the dose of relacorilant will be increased every 4 weeks by 100 mg, as tolerated and based on improvement in signs and symptoms of Cushing syndrome, to a target dose of 400 mg once daily (i.e., to 200 mg at Visit OL2, to 300 mg at Visit OL6, and to 400 mg at Visit OL10). Clinical benefit in the Open-Label Phase will be assessed by the Investigator either by a change from Baseline or change from the previous visit considering the following factors:
  - BP measurements and anti-hypertensive medications

  - Glucose levels and diabetes medication
  - Body weight and waist circumference
  - Cushingoid appearance and striae
  - Sit-to-stand test
  - Beck Depression inventory
  - Cushing Quality-of-Life questionnaire
- If all symptoms of Cushing syndrome present at Baseline have resolved, no dose escalation will occur beyond that visit.
- If any planned dose escalation is postponed, Visit OL14 can be used for a final dose escalation.
- Faster dose escalation during the open-label phase of the study for patients whose Cushing syndrome deteriorates may be allowed with medical monitor approval.
- If access of patients to the study site is restricted due to the COVID-19 pandemic, dose escalation up to 200 mg may occur remotely if necessary. Subsequent dose escalations, however, are permitted only after completion of safety assessments.
- Dose interruption, reduction and re-escalation are permitted for safety/tolerability.
  - The relacorilant dose can be reduced to a previous dose if it is not tolerated
  - Re-escalation after a dose reduction is permitted until Visit OL18.

3.1.3 Randomized-Withdrawal Phase (Randomization to Visit RW12)

3.1.3.1 Response Criteria

Patients who complete the OL phase and meet the following response criteria for DM/IGT or hypertension at Visit OL22 (see below and Section 3.6) will be randomized between Visit OL22 and up to 2 weeks after that visit in a 1:1 ratio to receive relacorilant or placebo for 12 weeks:

- **Patients with uncontrolled hypertension** at Baseline must meet one of the following response criteria:
  - ≥5 mm Hg decrease in mean systolic BP (SBP) and/or diastolic BP (DBP) from Baseline to Visit OL22, without worsening of either, based on 24-hour ambulatory BP monitoring (ABPM)

  Note: Increase of pre-existing blood pressure medication or initiation of new blood pressure medication, due to worsening in hypertension, disqualifies the patient from randomization into the RW phase. If a decrease in the BP medication occurred after the OL18 visit, reassess eligibility for randomization 4 weeks after the dose change.
- **Patients with DM/IGT** at Baseline must meet one of the following response criteria:

  In patients with DM

  - HbA1c has decreased by ≥0.5% from Baseline to Visit OL22
  - The 2-hour oGTT glucose is normalized (<140 mg/dL) or decreased by ≥50 mg/dL from Baseline to Visit OL22
  - Total daily insulin dose has decreased by ≥25% and HbA1c is unchanged or decreased compared with Baseline

In patients with IGT

– The 2-hour oGTT glucose is normalized (<140 mg/dL) from Baseline to Visit OL22

Note: Increase of pre-existing diabetes medication or initiation of new diabetes medication, due to worsening of hyperglycemia, disqualifies the patient from randomization into the RW phase. If a decrease in the insulin dose happened after Visit OL18, reassess eligibility for randomization 4 weeks after the dose change.

- **Patients with both DM/IGT and uncontrolled hypertension** at Baseline who do not meet the above-mentioned response criteria for both conditions must meet one of the following:
  – Meets one of the DM or IGT response criteria with no worsening in hypertension
  – Meets one of the uncontrolled hypertension response criteria with no worsening in DM or IGT
  – Worsening in hypertension is defined as ≥5 mm Hg increase in either systolic BP and/or diastolic BP from Baseline to Visit OL22.
  – Worsening in DM is defined as a ≥0.5% increase in HbA1c from Baseline to Visit OL22.
  – Worsening in IGT is defined as a ≥50 mg/dL increase in the 2-hour oGTT from Baseline to Visit OL22.
  – Patients who meet either the DM/IGT criteria or the uncontrolled hypertension criteria will be randomized in the respective strata.

  Note: Increase of pre-existing diabetes or blood pressure medication or initiation of new diabetes or blood pressure medication due to worsening hyperglycemia or hypertension, disqualifies the patient from randomization into the RW phase. If a decrease in insulin dose or BP medication occurred after Visit OL18, reassess eligibility for randomization 4 weeks after the dose change.

Randomization will be stratified to ensure balance in treatment assignment for patients that meet response criteria within the DM/IGT and hypertension subgroups (Section 9.1).

Treatment assignment and selected study assessments in the RW phase will remain blinded to the Investigators, the Sponsor, and the patients until after database lock.

No changes in the dose of study drug are allowed during the RW phase.

3.1.3.2 Rescue Criteria during Randomized Withdrawal Phase

2-hour oGTT and ABPM results during the RW Phase will be reviewed by an unblinded Medical Monitor to monitor patient safety. The unblinded Medical Monitor is unblinded to results of study assessments but is blinded to the treatment assignment.

- If a patient in the DM/IGT subgroup meets the first two of the following criteria, or if a patient in the hypertension subgroup meets the third criterion, the results will be communicated to the study site, and rescue medication may be initiated or increased as per Section 5.4.2.
  – Fasting glucose increases by 50 mg/dL from visit OL22, AND

  - 2-hour oGTT glucose increases by 100 mg/dL from Visit OL22
  - Increases in mean SBP or mean DBP by ABPM of more than 10 mm Hg from Visit OL22

Unblinding of the 2-hour oGTT or ABPM results will not result in the unblinding of study treatment.

In the event of rescue medication use before Visit RW12:

- In patients randomized to the DM/IGT subgroup, oGTT assessments will continue as planned until Visit RW12.
- In patients randomized to the hypertension subgroup, ABPM assessments will continue as planned until Visit RW12.

3.2 Patient Disposition

3.2.1 Patient Completion

- Patients who complete 12 weeks of the RW phase will return for the Follow-Up visit 28 days after the last dose of study drug. The Follow-Up visit will serve as the last study visit.
- Patients who complete 12 weeks of the RW phase, and entered an extension study within 28 days of the last dose of study drug, are not required to complete the Follow-Up visit. Visit RW12 will serve as the last study visit.

3.2.2 Early Termination

- Patients who complete Visit OL22, but do not meet a response criterion for randomization, will be instructed to discontinue study drug. The Follow-Up visit will be conducted 28 days after the last dose of study drug and will serve as the last study visit.
- If a patient discontinues early from the OL phase, the patient will complete an Early Termination visit at the time of last dose of study drug (or soon thereafter). The Follow-Up visit will be conducted 28 days after the last dose of study drug and will serve as the last study visit.
- If a patient discontinues early from the RW phase, the patient will be instructed to return for Visit RW12 per the patient's original dosing schedule as well as for the Follow-Up visit 28 days after the last dose of study drug. If RW12 is the return visit following early discontinuation from the RW phase, a 3-week visit window (2 weeks before the scheduled visit, 1 week after the scheduled visit) for RW12 is permitted.
- For patients who discontinue the study prior to the RW12 visit during the RW phase of the study and return for the RW12 visit, the follow up visit will be waived if the RW12 visit occurs at least 28 days after the last dose of administration of study drug.

3.2.3 Treatment Continuation

- Patients who complete the RW phase of the study will be permitted to continue relacorilant treatment in an extension study provided that they have at least 80% adherence with prescribed dosing (by capsule counts), and are, in the opinion of the Investigator, expected to maintain clinical benefit from the study drug. Clinical benefit

will be determined by the Investigator based on the changes during the Open-Label Phase in the following factors:
  - Hypertension
  - Hyperglycemia
  - Body weight and waist circumference
  - Clinical appearance
  - Sit-to-stand test
  - Psychiatric health and cognitive function
  - Cushing Quality-of-Life (QoL) score
- Patients who complete the OL phase of the study, but who do not meet a response criterion for randomization, will be permitted to continue relacorilant treatment in an extension study if, in the opinion of the Investigator, they have benefitted from the study drug and are expected to maintain that benefit as noted above. The same adherence rule applies.
- Patients who continue on to the extension study within 28 days of the last dose of study drug will not be required to complete the follow-up visit. The last study visit for these patients will be either the Visit OL22 (if criterion for randomization is not met) or Visit RW12 (if the RW phase was completed).

3.3 Number of Patients and Study Participation

3.3.1 Number of Patients

Approximately 162 patients are planned to enroll into a 6-month OL phase of the study to ensure the randomization of approximately 46 patients with hypertension into the subsequent 3-month, placebo-controlled RW phase.

Study enrollment will be monitored to ensure attainment of randomization targets. The number of patients enrolled in the OL phase may be adjusted to ensure a sufficient number of patients meeting response criteria to uncontrolled hypertension are randomized in the RW phase. Enrollment of patients may continue based on enrollment target projections.

The sample size calculation is described in Section 9.4.

3.3.2 Patient Study Participation

The maximum expected duration of a patient's participation is 46 weeks, including up to 6 weeks for Screening, 22–24 weeks of OL treatment, 12 weeks of double-blind treatment, and a Follow-up visit 4 weeks after the last dose of study drug. Based on the availability of all data, after the OL22 visit, there could be up to 2 weeks until a patient is randomized.

3.4 Definitions: End of Treatment and End of Study

3.4.1 End of Treatment

The end of treatment is defined as the date on which the patient received his or her last dose of study drug, which may be the end of the RW phase or earlier if the patient prematurely discontinues.

3.4.2 End of Study

The end of study is defined as the date of last contact (visit, telephone, e-mail) with any study patient. Corcept will ensure that the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and the regulatory authority(ies) are notified that the study has finished according to Corcept's standard operating procedures and/or local or national regulations.

3.5 Study Termination by Sponsor

If the Sponsor, Investigator, Study Monitor, or regulatory officials discover conditions arising during the study that indicate that the study should be halted or that the study site's participation should be terminated, this action may be taken after appropriate consultation between the Sponsor and Investigator. Conditions that may warrant termination of the study include, but are not limited to, the following:

- Discovery of an unexpected, serious, or unacceptable risk to the patients enrolled in the study.
- Decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product.

Study termination and follow-up will be performed in compliance with applicable regulations.

3.6 Study Endpoints

Endpoints for both OL and RW phases are listed below. In the RW phase, (1) endpoints related to hypertension will be analyzed in those patients who met any response criterion for hypertension at Visit OL22; and (2) endpoints related to DM/IGT will be analyzed in those patients who met any response criterion for DM/IGT at Visit OL22.

3.6.1 Primary Endpoints

The primary efficacy endpoint will be assessed in the RW phase. The study will be considered to have a positive outcome if the primary efficacy endpoint reaches statistical significance:

- **In patients with hypertension**, the proportion of patients with a loss of response with respect to hypertension from Visit OL22 to RW12 based on 24-hour ABPM as compared between relacorilant and placebo arms, where loss of response is defined as follows:
  - In patients who met only the SBP response criterion, an increase in SBP ≥5 mm Hg.
  - In patients who met only the DBP response criterion, an increase in DBP by ≥5 mm Hg.
  - In patients who met both the SBP and DPB response criteria, an increase in either SBP or DBP by ≥5 mm Hg.
  - Any increase or modification in antihypertensive medication due to worsening hypertension.
  - Patients discontinue treatment in RW phase for any reason.
- **In all patients**, assessment of safety based on TEAEs.

3.6.2 Secondary Efficacy Endpoints in the Randomized-Withdrawal Phase

- Loss of response (AUC-based) in DM/IGT subgroup with response at OL22: proportion of patients with a loss of response with respect to hyperglycemic control from Visit OL22 to RW12, as compared between relacorilant and placebo arms, where loss of response is defined as a ≥10% increase from baseline in $AUC_{glucose}$ from Visit OL22 to RW12, use of rescue medication (initiation or increase in diabetes medication due to worsening of hyperglycemic control), treatment discontinuation for any reason in RW phase, or patients with missing RW12 $AUC_{glucose}$ values.
- Mean change from Visit OL22 to RW12 in 24-hour average SBP as compared between relacorilant and placebo.
- Mean change from Visit OL22 to RW12 in 24-hour average DBP as compared between relacorilant and placebo.
- Mean change from Visit OL22 to RW12 in body weight as compared between relacorilant and placebo.
- In patients with DM/IGT, the mean change in $AUC_{glucose}$ from Visit OL22 to RW12 as compared between relacorilant and placebo arms.
- In patients with DM/IGT, the mean change in HbA1c from Visit OL22 to Visit RW12, as compared between relacorilant and placebo.
- Comprehensive loss of response in DM/IGT subgroup with response at OL22: proportion of patients with a comprehensive loss of response with respect to hyperglycemic control from Visit OL22 to RW12, as compared between relacorilant and placebo arms, where the comprehensive loss of response is defined as follows:

  In patients with DM:

  – Use of rescue medication (initiation or increase in diabetes medication due to worsening of hyperglycemic control), treatment discontinuation for any reason in RW phase, or loss to follow-up,

  OR

  – HbA1c has increased by ≥0.3% at Visit RW12 (compared to OL22),

  OR

  – The 2-hour time point of the plasma 2-hours oGTT glucose test at Visit RW12 is abnormal (≥140 mg/dL) and has increased by at least 50% of the reduction observed between Baseline and Visit OL22.

  In patients with IGT:

  – Use of rescue medication (initiation or increase in diabetes medication due to worsening of hyperglycemic control), treatment discontinuation for any reason in RW phase, or loss to follow-up,

  OR

  – The 2-hour time point of the plasma 2-hour oGTT glucose test at Visit RW12 is abnormal (≥140 mg/dL) and has increased by at least 50% of the reduction observed between Baseline and Visit OL22.

3.6.3 Exploratory Efficacy Endpoints in the Randomized Withdrawal Phase

Continuous Endpoints

- Mean change from Visit OL22 to RW12 in 24-hour average heart rate (HR) as compared between relacorilant and placebo (based on ABPM).
- Mean SBP, DBP, and HR at RW12 (end of dosing interval) as compared between relacorilant and placebo (based on ABPM).
- Mean difference in daytime and nighttime average SBP, DBP, and HR (based on ABPM) at Visit RW12 as compared between relacorilant and placebo.
- Mean change from Visit OL22 to Visit RW12 in body fat composition measured with DXA scan as compared between relacorilant and placebo.
- Mean change from Visit OL22 to Visit RW12 in Cushing Quality-of-Life (QoL) score as compared between relacorilant and placebo.
- In patients with DM (HbA1c at Baseline ≥6.5%), the mean change from Visit OL22 to Visit RW12 in HbA1c, as compared between relacorilant and placebo.
- In patients with IGT at Baseline, the mean change from Visit OL22 to Visit RW12 in the 2-hour glucose value of the plasma 2-hours oGTT test as compared between relacorilant and placebo arms.
- The mean change from Visit OL22 to RW12 as compared between relacorilant and placebo in the following: waist circumference; lean mass measured by DXA; serum osteocalcin; the Beck Depression Inventory®-II (BDI-II) score; sit-to-stand test score; trail-making test score; sex-hormone levels (estradiol, total and free testosterone, sex-hormone–binding globulin, follicle-stimulating hormone, and luteinizing hormone); FKBP5 and other potential biomarkers of GR activity; urinary free cortisol (UFC), late-night salivary cortisol and plasma adrenocorticotropic hormone (ACTH); $AUC_{insulin}$, Matsuda Index, homeostatic model assessment of insulin resistance (HOMA IR), and daytime and nocturnal average blood pressure.
- In patients with adrenal CS, the mean change in the ACTH levels from Visit OL22 to RW12 as compared between relacorilant and placebo.

Endpoints Summarized with Proportions

- For patients in the hypertension subgroup, the proportion of patients with any increase or modification in antihypertensive medication due to worsening hypertension from Visit OL22 to Visit RW12 as compared between relacorilant and placebo.
- Proportion of patients who worsened, as assessed by the Global Clinical Response from Visit OL22 to Visit RW12 (i.e., a score of –1 at Visit RW12 as compared with Visit OL22).
- For patients in the DM/IGT subgroup, the proportion of patients with any increase in dose of diabetes medication from Visit OL22 to Visit RW12 as compared between relacorilant and placebo.
- For patients in the DM subgroup, the proportion of patients who achieve 25% reduction in $AUC_{glucose}$ from Baseline OL to Visit RW12 as compared between relacorilant and placebo.
- In all patients randomized in the RW phase, proportion of patients with a loss of response with respect to hypertension or hyperglycemia from Visit OL22 to Visit RW12 based on

24-hour ABPM and $AUC_{glucose}$ as compared between relacorilant and placebo arms, where loss of response is defined as follows:

- In patients with hypertension only at Baseline OL:
  - In patients who met only the SBP response criterion, an increase in SBP ≥5 mm Hg.
  - In patients who met only the DBP response criterion, an increase in DBP by ≥5 mm Hg.
  - In patients who met both the SBP and DBP response criteria, an increase in either SBP or DBP by ≥5 mm Hg.
  - Any increase or modification in antihypertensive medication due to worsening hypertension.
  - Patients discontinue treatment in RW phase for any reason.
- In patients with DM/IGT only at Baseline OL:
  - A ≥10% increase from Baseline RW in $AUC_{glucose.}$from Visit OL22 to Visit RW12
  - Use of rescue medication (initiation or increase in diabetes medication due to worsening of hyperglycemic control).
  - Treatment discontinuation for any reason in RW phase.
  - Patients with missing RW12 $AUC_{glucose}$ values.
- In patients with hypertension and DM/IGT at Baseline OL, a loss of response will be defined as a loss of response with respect to either hypertension or hyperglycemic control (AUC-based) from Visit OL22 to Visit RW12, irrespective of which response criteria (hypertension or DM/IGT) they met to enter the RW phase.

3.6.4 Exploratory Efficacy Endpoints in the Open-Label Phase

Continuous Endpoints

- In patients with uncontrolled hypertension, the mean change in SBP from Baseline to Visit OL22/ET.
- In patients with uncontrolled hypertension, the mean change in DBP from Baseline to Visit OL22/ET.
- Mean change in Cushing Quality-of-Life (QoL) score from Baseline to Visit OL22.
- Mean change in body-fat composition from Baseline to Visit OL22/ET, as determined by DXA.
- Mean change in the Beck Depression Inventory®-II (BDI-II) score from Baseline to Visit OL22/ET.
- Mean change in body weight from Baseline to Visit OL22/ET.
- In patients with IGT, the mean change in 2-hour oGTT glucose from Baseline to Visit OL22/ET.
- In patients with DM (HbA1c ≥6.5% at Baseline), the mean change in HbA1c from Baseline to Visit OL22/ET.
- In patients with DM/IGT, the mean change in $AUC_{glucose}$ from Baseline to Visit OL22/ET.

- The mean change from Baseline to Visit OL22/ET in the following: waist circumference; lean mass measured by DXA; serum osteocalcin; the Beck Depression Inventory®-II (BDI-II) score; sit-to-stand test score; trail-making test score; sex-hormone levels (estradiol, total and free testosterone, sex-hormone–binding globulin, follicle-stimulating hormone, and luteinizing hormone); FKBP5 and other potential biomarkers of GR activity; urinary free cortisol (UFC), late-night salivary cortisol and plasma adrenocorticotropic hormone (ACTH); $AUC_{insulin}$, Matsuda Index, homeostatic model assessment of insulin resistance (HOMA IR), and daytime and nocturnal average blood pressure.
- In patients with adrenal Cushing syndrome (CS), the mean change in ACTH levels from Baseline to Visit OL22/ET.

Endpoints Summarized with Proportions

- In patients with hypertension, the proportion of patients who meet any of the hypertension response criteria at Visit OL22/ET.
- In patients with hypertension, the proportion of patients with reduction or discontinuation of antihypertensive medications from Baseline to Visit OL22/ET.
- The proportion of patients with a positive Global Clinical Response score at Visit OL22/ET.
- In patients with DM/IGT, the proportion of patients who meet any of the DM/IGT response criteria at Visit OL22/ET.
- In patients with IGT, the proportion of patients who achieved normalization of glucose based on the plasma 2-hours oGTT test and/or a reduction in the 2-hour glucose by 50 mg/dL from Baseline to Visit OL22/ET.
- In patients with DM (HbA1c ≥6.5% at Baseline), the proportion of patients with any decrease in dose of diabetes medication from Baseline to Visit OL22/ET.
- The proportion of patients meeting any DM/IGT or hypertension response criterion at Visit OL22/ET by dose at which response was first reached.
- In patients with DM/IGT, the proportion of patients with ≥25% decrease in $AUC_{glucose}$ from Baseline to Visit OL22/ET.
- In patients with DM/IGT, the proportion of patients with ≥0.5% decrease in HbA1c from Baseline to Visit OL22/ET.

3.6.5 Exploratory Pharmacokinetic Endpoints

- In patients with endogenous Cushing syndrome, the steady-state plasma exposures of relacorilant (additional details will be summarized in the PK Analysis Plan).

4 STUDY POPULATION

This study includes patients with endogenous Cushing syndrome and associated DM/IGT and/or uncontrolled hypertension.

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

Possible etiologies of Cushing syndrome include Cushing disease, ectopic ACTH-secreting, ectopic corticotropin releasing hormone-secreting tumors, adrenal cortisol-secreting adenomas, adrenocortical carcinoma, primary pigmented nodular adrenal disease, and primary macronodular adrenal hyperplasia.

4.1 Inclusion Criteria

Each patient must meet all of the following criteria to be enrolled in the study:

Inclusion Criteria

To enroll in the study, each patient must meet the following key inclusion criteria:

1. Male or female, 18 to 80 years of age, inclusive.
2. Has a confirmed biochemical diagnosis of endogenous Cushing syndrome based on the presence of at least 2 of the following (Nieman et al. 2008):
    - UFC >upper limit of normal (ULN) in at least 2 complete 24-hour tests within the screening window.
    - Late night salivary cortisol >ULN in at least 2 tests (using a salivette) within the screening window (Note: Test is not appropriate for night-shift workers and cannot be used to evaluate eligibility).
    - Lack of cortisol suppression (>1.8 µg/dL serum cortisol) on either 1mg overnight or 2 mg 48-hour dexamethasone suppression testing during Screening, or within 12 weeks before signing the informed consent.
3. Has at least 2 of the following clinical signs and symptoms of Cushing syndrome:
    - Bodily characteristics of a Cushingoid appearance (e.g., facial rubor, moon facies, dorsocervical fat pad, supraclavicular fat pad).
    - Increased body weight or central obesity.
    - Proximal muscle weakness.
    - Low bone mass based on DXA scan.
    - Psychiatric symptoms (including depression or psychosis).
    - Skin manifestations: violaceous striae, acne, and/or hirsutism.
    - Easy bruisability.
4. Has at least 1 of the following at Baseline:

- DM (fasting plasma glucose ≥126 mg/dL and/or 2-hour oGTT plasma glucose ≥200 mg/dL at 2 hours or HbA1c ≥6.5%), or IGT (plasma glucose ≥140 mg/dL and <200 mg/dL on a 2-hour oGTT glucose) (American Diabetes Association 2020).
- Uncontrolled hypertension (mean SBP ≥135 to ≤170 mm Hg and/or mean DBP ≥85 to ≤110 mm Hg) based on 24hour ABPM (Parati et al. 2014).

5. If receiving medical treatment for DM/IGT or hypertension, there has been no increase in medication dosage for at least 4 weeks prior to Baseline assessment.
6. If receiving medical treatment for depression, there has been no increase in medication dosage for at least 6 weeks prior to Baseline.
7. For women of childbearing potential, has a negative serum pregnancy test at Screening and negative urine pregnancy test at Baseline.

4.2 Exclusion Criteria

Patients who meet any of the following criteria will not be permitted entry to the study:

1. Has severe, uncontrolled hypertension (mean SBP >170 mm Hg or mean DBP >110 mg at Screening), based on 24-hour ABPM.
2. Has poorly controlled DM (HbA1c >12% at Screening).
3. Has a known "long term" history of both hypertension and diabetes (defined as both hypertension and diabetes diagnosed >10 years prior to the initial diagnosis of endogenous CS).
4. Has a history of cyclic Cushing's syndrome with fluctuating clinical manifestations.
5. Has DM Type 1.
6. Has abnormal liver test results (total bilirubin >1.5×ULN or elevated alanine aminotransferase or aspartate aminotransferase >3×ULN at Baseline).
7. Has severe renal insufficiency (glomerular filtration rate ≤29 mL/min at Baseline).
8. Has uncontrolled, clinically significant hypothyroidism or hyperthyroidism.
9. Has prolonged QT interval corrected for heart rate using Fridericia's equation (QTcF) (>450 ms for men and >470 ms for women) with normal QRS interval (<120 ms) or QTcF interval >500 ms with wide QRS interval (≥120 ms).
10. Has received stereotactic radiation therapy for a Cushing syndrome-related tumor within 24 months of Baseline or conventional pituitary radiation therapy within 36 months of Baseline.
11. Has undergone pituitary surgery <3 months prior to Screening.
12. Has used or plans to use any of the following treatments for Cushing syndrome within 4 weeks prior to Baseline:

    - Mifepristone
    - Adrenostatic medications: metyrapone, osilodrostat, ketoconazole, fluconazole, aminoglutethimide, or etomidate

- Serotonin antagonists: cyproheptadine, ketanserin, or ritanserin
- Dopamine agonists: bromocriptine or cabergoline
- Gammaaminobutyric acid agonists: sodium valproate
- Short-acting somatostatin analogs: octreotide, lanreotide, or pasireotide.

13. Has used or plans to use somatostatin receptor ligands: long-acting octreotide or pasireotide within 8 weeks prior to Baseline.
14. Patients who require inhaled glucocorticoid use and have no alternative option if their condition deteriorates during the study.
15. Has adrenocortical carcinoma.
16. Has used mitotane prior to Baseline.
17. Has ectopic Cushing syndrome and a life expectancy of <3 years or receiving chemotherapy.
18. Has pseudo-Cushing syndrome. Patients with known or suspected pseudo-Cushing 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 et al. 1993, Giraldi et al. 2007, Yanovski et al. 1998) to rule-in or rule-out this possibility.
19. Has taken any investigational drug within 4 weeks prior to Baseline, or within less than 5 times the drug's half-life, whichever is longer.
20. Ongoing use of antidiabetic, antihypertensive, antidepressant, or lipid-lowering medications that are highly dependent on CYP3A for clearance and that cannot undergo dose modification upon coadministration with strong CYP3A inhibitors.
21. Ongoing use of any strong CYP3A4 inducer or any other prohibited medications (Section 5.4.4).
22. Is pregnant or lactating.
23. Is a female patient 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) who cannot use a highly effective method of contraception (Section 4.6.2).
24. Has an acute or unstable medical problem that could be aggravated by treatment with the investigational study drug.
25. Has a history of hypersensitivity or severe reaction to the study drug, to a similar class of drug, or to the study drug's excipient.
26. In the Investigator's opinion, should not participate in the study or may not be capable of following the study schedule.
27. Has known HIV or hepatitis B or C infection.
28. Is a family member of one of the Sponsor's employees, the Investigator, or the site staff directly working on the study.
29. Has a history of unexplained vaginal bleeding or unexplained endometrial abnormalities.

4.3 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently entered in the study.

Patients who fail Screening due to a laboratory result may be retested within the Screening period without prior Corcept approval. Other laboratory tests, not directly impacting patient eligibility, during the Screening period may be repeated at the Investigator's discretion. The 24-hour ABPM may be repeated if there is a technical problem with the test.

Whenever patients are rescreened, they must sign an informed consent form (ICF) each time. The Screening assessments that do not need to be repeated during rescreening are the 2-hour oGTT glucose (if performed within 2 weeks of the Baseline Visit) and the dexamethasone suppression test (if performed within 12 weeks of consent).

4.4 Early Patient Discontinuation or Withdrawal

Patients may withdraw their consent to participate in the study at any time for any reason without prejudice. The Investigator should make a reasonable attempt to document the specific reason why consent is withdrawn.

The Investigator also has the right to withdraw patients from the study for the following reasons:

The Investigator decides it is in the patient's best interest to discontinue study drug and/or participation in the study. Reasons may include, but are not limited to, the patient requiring or starting a prohibited medication(s), or not adhering to protocol procedures.

- The patient experiences an AE or any of the special safety events outlined in Table 2, Section 5.3.1 that the Investigator believes requires withdrawal from the study.
- Patient becomes 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.
- Patients whose Cushing syndrome deteriorates during the open-label phase of the study on the maximum tolerated dose of relacorilant.
- Patients whose Cushing syndrome deteriorates significantly during the RW phase and cannot be controlled with symptomatic management of the comorbidities until the RW12 visit.

Patients who discontinue study drug early should be encouraged to complete the end-of-treatment and follow-up assessments and to report any AEs, including SAEs, for 28 days after the last administration of study drug. The date when the patient discontinues study drug and the reason for discontinuation must be recorded on the electronic case report form (eCRF).

For patients who withdraw consent to participate in the study, every effort should be made to determine whether the withdrawal of consent was related to an AE or a specific aspect of the study. If a patient wishes to withdraw consent to further participation in the study entirely—including follow-up, this should be clearly documented (1) in the patient's medical record and signed by the Investigator and (2) in the eCRF.

Before a patient is determined to be lost to follow-up, reasonable efforts (i.e., 3 documented attempts) will be made to contact the patient and complete study termination procedures.

For guidelines about temporary interruption of study drug or study-drug modifications, see Section 5.3.

4.5 Replacement of Patients

The proportion of patients who complete the OL phase and are randomized in the RW phase will be reviewed periodically. To maintain sufficient power to detect treatment difference, the number of patients enrolled in the OL phase may be adjusted to ensure a sufficient number of patients meeting response criteria to DM/IGT and/or uncontrolled hypertension are randomized in RW phase.

4.6 Restrictions During Study

The following restrictions apply to patients in this study (prohibited medications are described in Section 5.4.4).

4.6.1 Dietary Restrictions

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. Each dose should be taken with 240 mL water.

Patients must abstain from grapefruit, grapefruit juice, or grapefruit-containing products during the study.

4.6.2 Contraception

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 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 (e.g., 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, male patients should not donate sperm until 30 days after the last dose of study drug.

4.6.3 Radiation Therapy and Radiation Surgery

Patients may not undergo conventional pituitary radiation therapy or stereotactic pituitary radiation therapy (e.g., gamma knife radiosurgery) during the study.

5 STUDY TREATMENTS AND MANAGEMENT

Study drug is defined as relacorilant (during the OL phase) and relacorilant or placebo (RW phase).

5.1 Study Drug and Placebo

Relacorilant and placebo equivalent, including dose and regimen, formulation, packaging, and storage, are described in Table 1.

Table 1 Study Drug and Placebo: Formulation, Administration, Packaging, and Storage

Specifications	Study Drug and Placebo	
	Relacorilant	**Placebo**
Description	For each capsule, relacorilant is prepared as a [redacted]	The placebo for relacorilant capsule is designed to match the study drug in appearance. Each placebo capsule contains a formulation of [redacted]
Supplied	Capsules, 30-count in a white bottle with induction seal and child-resistant closure and labeled as required per country requirement.	Capsules, 30-count in a white bottle with induction seal and child-resistant closure and labeled as required per country requirement.
Appearance	Yellow, oblong, [redacted] capsules	Yellow, oblong [redacted] capsules
Unit dose strength	100 mg relacorilant/capsule	Placebo equivalent
Dose levels	100, 200, 300, or 400 mg	Placebo equivalent
Administration	Orally, with 240 mL of water under fasted conditions	Orally, with 240 mL of water under fasted conditions
Regimen	1–4 capsules, once daily	1–4 capsules, once daily
Restrictions	Refer to Section 4.6.1	Refer to Section 4.6.1
Dispensing study drug	Dispense to patients at the visits specified in Appendix A	Dispense to patients at the visits specified in Appendix A
Storage	Store as follows: • In a secure location • At [redacted], excursions permitted [redacted] • Out of reach and sight of children	Store as follows: • In a secure location • At [redacted] excursions permitted [redacted] • Out of reach and sight of children

Note: Procedures for inventory, reconciliation, and destruction or return of study drug are provided in Section 11.5.

5.2 Dose-Escalation Process

- The starting dose at Baseline will be 100 mg relacorilant once daily for 2 weeks.

During dose escalation, all patients will be escalated in a stepwise manner from 100 mg to 400 mg once daily, based on tolerability and improvement in hypertension and/or hyperglycemia. The starting dose at Baseline will be 100 mg relacorilant once daily for 2 weeks, after which the dose will be increased to 200 mg. Then the dose will increase in 100 mg increments every 4 weeks. Dose escalation will be performed based on tolerability considering the following factors (only in patients whose current dose is well tolerated).

In patients with hypertension only, the mean 24-hour BP (based on ABPM):

- SBP is ≥130 mm Hg or
- SBP is <130 mm Hg and has not decreased by ≥5 mm Hg from Baseline.
- DBP is ≥80 mm Hg or
- DBP is <80 mm Hg and has not decreased by ≥5 mm Hg from Baseline.

In patients with DM/IGT only, the 2-hour glucose based on oGTT:

Note: For visit OL2, the fasting glucose assessment from the Chemistry laboratory panel will be used for dose escalation purposes.

- is ≥140 mg/dL or fasting glucose is >100 mg/dL or
- is <140 mg/dL and has not decreased by ≥30 mg/dL from Baseline.

In patients with both DM/IGT and hypertension:

The mean 24-hour BP (based on ABPM):

- SBP is ≥130 mm Hg or
- SBP is <130 mm Hg and has not decreased by ≥5 mm Hg from Baseline.
- DBP is ≥80 mm Hg or
- DBP is <80 mm Hg and has not decreased by ≥5 mm Hg from Baseline.

AND

- is ≥140 mg/dL or fasting glucose is >100 mg/dL or
- is <140 mg/dL and has not decreased by ≥30 mg/dL from Baseline.
- Dose escalation may be held if the patient cannot safely tolerate escalation to the next dose.
- Faster dose escalation for patients whose Cushing syndrome deteriorates during the study may be allowed on a case-by-case basis after discussion and approval by the medical monitor.
- If any planned dose escalation is postponed, Visit OL14 can be used for a final dose escalation.
- If access of patients to the study site is restricted due to the COVID-19 pandemic, dose escalation up to 200 mg may occur remotely if necessary. Subsequent dose escalations, however, are permitted only after completion of safety assessments.
- Dose escalations start the day after the Visit at which they are approved by the Investigator.

- After normalization of hypertension and/or hyperglycemia, further dose escalation will be allowed considering the following factors:
- Body weight and waist circumference
- Cushingoid appearance and striae
- Sit-to-stand test
- Beck Depression inventory
- Cushing Quality-of-Life questionnaire
- If all symptoms of Cushing syndrome present at Baseline have resolved, no dose escalation will occur beyond that visit

5.3 Dose Modifications

Every effort should be made to administer study drug on the planned dose and schedule.

Dose interruption, or reduction and re-escalation, are permitted for safety/tolerability, as follows:

- Dose interruptions or reductions may occur at any time, including between visits, during the OL phase.
- No changes in the dose of study drug are allowed during the RW phase.
- Re-escalation after a dose reduction is permitted, with the approval of the Medical Monitor, until Visit OL18 (so that the OL period ends on a stable dose).
- During study-drug interruptions, patients will continue on the same visit schedule.

Dose reductions to manage excessive GR antagonism are outlined in Section 5.3.1.

5.3.1 Dose Interruption and/or Discontinuation: Special Safety Events

Based on the mechanism of action of relacorilant, there is a theoretical risk of excessive GR antagonism, which could manifest with findings such as weakness, tiredness, dizziness, hypoglycemia, dehydration, weight loss, nausea, vomiting, diarrhea, or muscle aches. Because relacorilant does not affect the mineralocorticoid receptor, it is unlikely that hypotension would occur in the absence of antihypertensive medication.

The actions outlined in Table 2 should be taken if a patient:

- Exhibits signs and symptoms of excessive GR antagonism.
- Experiences significant trauma, surgery, or medical illness occurring at any time during the study (through 2 weeks after last dose).

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

- Mention use of relacorilant (“glucocorticoid receptor antagonist”).
- Potential need for glucocorticoid use in setting of shock, surgery, serious illness, or injury.
- Recommended dose of replacement steroids (4 to 10 mg dexamethasone intramuscularly or intravenously).
- Investigator contact information.

Table 2 Criteria for Dose Modification or Discontinuation Due to Special Safety Events (Until Visit OL18)

	Criteria for Interrupting and Restarting or Modifying Study Drug and Patient Management	**Criteria for Stopping Study Treatment**
Excessive GR antagonism	**Criteria**: Signs and symptoms of excessive GR antagonism **Management:** • Immediately interrupt relacorilant treatment for at least 3 days and start standard supportive care, including fluid resuscitation, as indicated. • If appropriate, administer supplemental glucocorticoids given in high doses to overcome the GR antagonism produced by relacorilant. Initially, consider parenteral dexamethasone (4 to 10 mg), 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, consider discontinuing it or adjusting the dose, particularly in the presence of hypotension. • Restart relacorilant treatment only if the potential benefits outweigh the risks and after a discussion with the Medical Monitor. – Restart relacorilant at the lowest tolerable dose previously administered to the patient. – After 2 weeks, resume the current dose or increase by 100 mg with the approval of the Medical Monitor.	A combination of at least 2 of the following Grade 3 or higher events can lead to stopping/reducing dose: fatigue, anorexia, nausea/vomiting[a] (associated with decreased oral intake), or abdominal pain, seen either at the 200-mg dose level or at other dose levels for which the Investigator deems dose reduction is not an option.
Significant trauma, surgery, or medical illness at any time during the study (through 2 weeks after last dose)	**Management:** • As medically indicated, interrupt relacorilant treatment and provide supplemental glucocorticoids to offset the glucocorticoid receptor antagonism even in patients not experiencing signs and symptoms of excessive antagonism. • After resolution of the physiological stress associated with the event and if still within the Treatment Period, resume relacorilant at the last dose level the patient was receiving before interruption.	

GR, glucocorticoid receptor.
[a] For the purpose of this assessment, nausea and vomiting are considered 1 criterion.

In the event of study-drug discontinuation before Visit RW12:

- In patients randomized to the DM/IGT subgroup, oGTT assessments will continue as planned until Visit RW12.
- In patients randomized to the hypertension subgroup, ABPM assessments will continue as planned until Visit RW12.

5.4 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, and/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 drug 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.

Patients are prohibited from taking antidiabetic, antihypertensive, antidepressant and/or lipid-lowering medications that are highly dependent on CYP3A for clearance and cannot undergo dose modifications on coadministration with strong CYP3A inhibitors. For example, the FDA provides a current list of Substrates, Inhibitors and Inducers of CYP3A at the following website.

https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm#table4-1

The list may not be inclusive of all currently available Substrates, Inhibitors and Inducers of CYP3A worldwide. The Investigator should contact the Medical Monitor with any questions.

Patients on such medications at Screening will need to be switched to an alternative antidiabetic, antihypertensive, antidepressant, or lipid-lowering medications and be on a stable dose of the alternative medication for at least 4 weeks to be eligible to participate in this study.

Information about concomitant medications will be collected from all patients at each visit from Screening through the Follow-up Visit. If access of patients to the study site is restricted due to the COVID-19 pandemic, a review of concomitant medications may involve alternative methods (e.g., phone contact or virtual study visits). Any changes in medications since the last visit will be captured and recorded.

Efficacy assessments include the total daily dose of insulin for patients with DM/IGT and antihypertensive medications for patients with uncontrolled hypertension.

5.4.1 Rules for Antidiabetic and Antihypertensive Medication Use During the Open-Label Phase

In patients with DM/IGT at Baseline:

- Medication for control of blood glucose should be maintained at a stable dose.

- Patients should not take antidiabetic medications before the oGTT; they may be taken with food after the oGTT. Long-acting insulin may be taken the prior evening.
- Reduction or discontinuation of insulin and insulin secretagogues should be considered only if fasting or postprandial blood glucose is <70 mg/dL on at least 2 home measurements or 1 serum glucose measurement associated with symptoms of hypoglycemia.
  - For basal and prandial insulin, consider decreasing dosage by 20%.
  - For insulin secretagogues, consider decreasing dosage by 50%; discontinue if recurrent.
  - Reductions of insulin and/or insulin secretagogues can be adjusted depending on the degree of hypoglycemia and the current total dose of insulin.
- In patients with hypoglycemia unawareness, changes in insulin and insulin secretagogues should be considered if fasting or postprandial glucose is <70 mg/dL on at least 2 home measurements or 1 serum glucose measurement.
- If any modification of existing diabetes medications, or initiation of new diabetes medication is being considered, a 2-hour oGTT glucose should be obtained prior to modification of medications.

In patients with uncontrolled hypertension at Baseline:

- Antihypertensive medications should be maintained at a stable dose.
- Reduction or discontinuation should be considered only if:
  - Blood pressure decreases below 100 mm Hg systolic or 60 mm Hg diastolic by ABPM
  - Symptoms of hypotension (including orthostatic hypotension) occur.
- In patients in whom a reduction or discontinuation of antihypertensive medication is being considered, an ABPM should be performed prior to modification of medications. The measurement from the last ABPM prior to dose modification will be used in the primary study analysis.

5.4.2 Rules for Antidiabetic and Antihypertensive Medication Use During the Randomized-Withdrawal Phase

In patients with DM/IGT at Baseline:

- Medication for control of blood glucose should be maintained at a stable dose.
- Patients should not take antidiabetic medications before the oGTT; they may be taken with food after the oGTT. Long-acting insulin may be taken the prior evening.
- Reduction or discontinuation of insulin and insulin secretagogues should be considered only if fasting or postprandial blood glucose <70 mg/dL on at least 2 home measurements or 1 serum glucose measurement associated with symptoms of hypoglycemia
  - For basal and prandial insulin, consider decreasing dosage by 20%.
  - For insulin secretagogues, consider decreasing dosage by 50%; discontinue if recurrent.
  - Reductions of insulin and/or insulin secretagogues can be adjusted depending on the degree of hypoglycemia and the current total dose of insulin.

- In patients with hypoglycemia unawareness, changes in insulin and insulin secretagogues should be considered if fasting or postprandial glucose is <70 mg/dL on at least 2 home measurements or 1 serum glucose measurement.
- If any modification of existing diabetes medications or initiation of new diabetes medication is being considered, a 2-hour oGTT glucose should be obtained prior to modification of medications.
- The unblinded Medical Monitor will notify the site if fasting or postprandial values from the 2-hour oGTT are below 70 mg/dL. Unblinding of fasting or postprandial glucose from the 2-hour oGTT will not result in the unblinding of study treatment.

Rescue criteria during the RW phase

- 2-hour oGTT results during the RW Phase will be reviewed by an unblinded Medical Monitor to monitor patient safety.
  - If a patient meets the following criteria, the results will be communicated to the study site, and rescue medication may be initiated or increased.
    - Fasting glucose increases by 50 mg/dL from visit OL22, AND
    - 2-hour oGTT glucose increases by 100 mg/dL from Visit OL22
- Unblinding of the 2-hour oGTT will not result in the unblinding of study treatment.
- If antidiabetic medication is increased or initiated during the RW phase, oGTTs will be performed up to RW12 visit.

In patients with uncontrolled hypertension at Baseline:

- Antihypertensive medications should be maintained at a stable dose.
- Reduction or discontinuation of antihypertensive medications should be considered only if:
  - Blood pressure decreases below 100 mm Hg systolic or 60 mm Hg diastolic by office measurement on at least two measurements obtained 15 min apart with symptoms of orthostatic hypotension.
  - Symptoms of hypotension (including orthostatic hypotension) occur
- The unblinded Medical Monitor will notify the site if BP decreases below 100 mm Hg mean SBP or 60 mm Hg mean diastolic by ABPM.
- Unblinding of ABPM results will not result in the unblinding of study treatment.
- If any modification of existing antihypertensive medication or initiation of new antihypertensive medication is being considered, an ABPM should be performed prior to modification of medications.

Rescue criterion during the RW phase

- ABPM results during the RW Phase will be reviewed by an unblinded Medical Monitor to monitor patient safety.
  - If a patient meets the following criterion, the results will be communicated to the study site, and rescue medication may be initiated or increased.
    - Increases in mean SBP or mean DBP by ABPM of more than 10 mm Hg from Visit OL22.
- Unblinding of ABPM results will not result in the unblinding of study treatment.

- If antihypertensive medication is increased or initiated during the RW phase, ABPM tests will be performed up to RW12 visit.

5.4.3 Rules for Other Permitted Concomitant Medications

- Lipid-lowering drugs: No increases in dose are allowed from 4 weeks before Baseline through the Follow-up Visit, unless clinically necessary.
- Antidepressant drugs: No increases in dose are allowed from 6 weeks before Baseline through the end of study-drug dosing, unless clinically necessary.

5.4.4 Prohibited Medications

Relacorilant is a strong inhibitor of CYP3A. Medications that are highly dependent on CYP3A for clearance for which elevated plasma concentrations are associated with SAEs and for which dose modification is not an option with strong CYP3A inhibitors should be avoided (consult the prescribing information of the respective concomitant medications for further details).

Additionally, the following medications used in the treatment of Cushing syndrome are prohibited during treatment with study drug in this study:

- Adrenostatic medications: metyrapone, osilodrostat, ketoconazole, fluconazole, aminoglutethimide, mitotane, 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, octreotide long-acting release, pasireotide, pasireotide long-acting release, lanreotide), and mifepristone.
- Strong CYP3A inducers.
- Antidiabetic, antihypertensive, antidepressant, and/or lipid-lowering medications that are highly dependent on CYP3A for clearance and cannot undergo dose modifications upon coadministration with strong CYP3A inhibitors.
- Systemic corticosteroids [with exception of temporary use for treatment of excessive GR antagonism], potent (group III) topical corticosteroids in extended body surface areas, and intra-articular corticosteroids unless other treatment options fail/contraindicated.
- Other investigational agents.

5.5 Method of Treatment Assignment and Randomization

At the Randomization visit, patients meeting response criteria described in Section 3.1 will be randomized 1:1 to continue their dose of relacorilant from the OL phase or to receive placebo. Patients switched to placebo will continue taking the same number of capsules per dose.

Randomization of patients will be stratified by one factor (i.e., response at Visit OL22) with 3 levels:

- Response by DM/IGT criteria only
- Response by hypertension criteria only
- Response by DM/IGT and hypertension criteria

The randomization visit will be scheduled once all laboratory test data and ABPM results are available to determine eligibility.

Randomization will be centrally assigned using an interactive web response system (IWRS). The telephone number and call-in directions for the IWRS and/or the log-in information and directions for the IWRS will be provided to each site.

Study drug will be dispensed at the study visits summarized in Summary of events (Appendix A). Returned study drug should not be re-dispensed to the patients.

Statisticians involved in generation of randomization codes, or who have access to the randomization code will not be involved in the analyses of the study.

5.6 Blinding/Unblinding

The Sponsor or designee, the Investigator, the blinded Medical Monitor, study-site personnel, and the patient will be blinded to treatment assignment. Selected study-assessment and laboratory results (as described in Section 6) from the RW phase that could potentially reveal the treatment assignment will remain blinded until after database lock.

To maintain the overall quality and blinding of the clinical trial, unblinding of treatment assignment should occur only in exceptional circumstances.

If unblinding treatment assignment is deemed necessary, the Investigator should complete the unblinding process through the [redacted]) or, if the [redacted] is unavailable, contact the below emergency unblinding toll-free number provided below and in the study manual. The Investigator should notify the Sponsor of any unblinding occurrences.

[redacted]

Investigators wishing to discuss potential unblinding should contact the Medical Monitor for further discussion.

If unblinding of either central lab or ABPM data is required, the site should refer to the respective manual for the unblinding process.

Note: Even if lab values or ABPM values are unblinded, the treatment assignment will remain blinded.

The Investigator is encouraged to maintain the blind as far as possible. The patient's treatment assignment must not be disclosed to the patient and/or other study staff. There should not be any written or verbal statements of the patients' treatment assignment in any patient documents.

If any accidental unblinding occurs for treatment assignment or blinded laboratory/ABPM values, the Investigator should promptly document the occurrence and notify the Sponsor.

5.7 Dosing Diary

A dosing diary will be dispensed at the time points specified in Appendix A for patients to record each self-administered dose of study drug and any concomitant medications. Entries should include the number of capsules as well as the date and time of study-drug administration. Time and dose administered should be documented in the clinic charts.

Patients will be instructed to return all unused study drug and the dosing diary at the patient visits.

5.8 Product Accountability and Treatment Adherence

Study drug will be dispensed to each patient at applicable visits as outlined in the schedule of assessments. Sufficient study drug will be provided for the period between study visits. To mitigate the potential of patients not being able to return for scheduled study visits due to the COVID-19 pandemic, additional study drug may be dispensed.

The Investigator is responsible for the accountability of all used and unused study drug. 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 bottles 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 study drug to be used other than as directed by the protocol.

Adherence to the study-drug regimen will be determined by review of the dosing diary and counting the number of capsules taken and returned at each study visit.

5.9 Continued Access to Study Treatment

All patients completing the study will be eligible for rollover to the extension study, provided that they have had at least 80% adherence to prescribed dosing, according to capsule counts, and are expected to maintain or receive clinical benefit from relacorilant, in the opinion of the Investigator.

5.10 External Data Review Committees

5.10.1 Data Review Board for Evaluation of Global Clinical Response

The Global Clinical Response will be evaluated by a 3-member Data Review Board (DRB) that has expertise in Cushing syndrome. Each member of the DRB will independently review, assess, and assign a single overall clinical score of worsening, no change, or improvement. Details of the of the evaluation of this endpoint and the meeting frequency and composition of the DRB will be specified in the DRB charter.

5.10.2 Independent Data Monitoring Committee to Monitor Patient Safety

An Independent Data Monitoring Committee (IDMC) will be established to conduct periodic reviews of data to ensure the safety of patients. The IDMC will be composed of at least 3 voting members: two physicians and one statistician. The IDMC will meet at least quarterly. Further details describing the IDMC composition, contents of data reports, responsibilities, and decision rules will be described in the IDMC Charter.

6 DESCRIPTION OF STUDY ASSESSMENTS AND PROCEDURES AND APPROPRIATENESS OF MEASUREMENTS

Study procedures and their timing are summarized in the Schedule of Events (SOE; Appendix A).

The Investigator and Sponsor will conduct the study in accordance with International Council for Harmonisation (ICH) GCP and local regulations. Adherence to the study design requirements, including those specified in the SOE, is essential and required for study conduct, and the Investigator must ensure that study procedures are performed as described in the protocol. During the study, procedures and observations will be monitored to confirm that study requirements are being followed, as outlined in the SOE.

In the event that a patient is unable to come to the clinic to participate in study-related visits or procedures due to the COVID-19 pandemic, Sponsor-approved alternative options may be provided to the Investigator sites based on the needs and safety of patients. This may include the provision of study drug dispensation and delivery outside of the clinic.

6.1 Informed Consent and Screening

Prior to performing any study-related procedures, the patient must sign and date an IRB-approved- ICF (Section 10.3.1 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 sign consent up to 6 weeks prior to the first dose of study drug on Day 1. Remote consenting will be permitted if access of patients to the study site is restricted due to the COVID-19 pandemic. IRB guidelines should be followed.

All Screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for Screening failure (Section 4.3), as applicable. Screening assessments performed during the 6-week screening window can be used as Baseline data, and assessments do not need to be repeated (with the exception of the 2-hour oGTT glucose test, HbA1c, and ABPM, which must be performed within 2 weeks of the Baseline Visit) and unless otherwise noted. Eligibility criteria will be confirmed at Baseline.

6.1.1 Dexamethasone Suppression Test

The dexamethasone suppression test (DST) should be performed during Screening if an additional test is required to confirm endogenous Cushing syndrome (e.g., if either the 24-hour UFC or late-night salivary test results are within normal range, the dexamethasone suppression test is required to confirm Cushing syndrome). Dexamethasone will be administered either as a 1-mg dose overnight or a 2-mg dose over 48 hours; a blood sample will be drawn and will be tested at a local laboratory.

Patients who had a DST performed within 12 weeks prior to the ICF date are not required to repeat the test at Screening.

6.2 History

6.2.1 Cushing-Syndrome–Medication Washout

Medications used in the treatment of Cushing syndrome are prohibited and require washout (as applicable) during Screening, provided the intervals specified in Exclusion Criteria 12 and 13 fit within the Screening window. Patients requiring washout of a medication for Cushing syndrome must complete the Screening/Baseline oGTT, HbA1c, and 24-hour ABPM tests after washout and within 2 weeks before Day 1 dosing; 24-hour UFC tests, and salivary cortisol tests must be completed after washout.

6.2.2 Demographics and Baseline Disease Characteristics

Patient demographic data, including age, sex, race, and ethnicity, and Baseline disease characteristics, such as years since diagnosis and Cushing syndrome type (e.g., ectopic ACTH secretion, primary pigmented nodular adrenocortical disease, primary macronodular adrenal hyperplasia), will be documented at Screening.

6.2.3 Medical and Medication History

Patient medical history, including the diagnosis, etiology, and treatment history of Cushing syndrome (including dexamethasone suppression test failure where appropriate), diagnosis of DM/IGT and/or hypertension, as well as other illnesses and allergies, date(s) of onset, and whether conditions are currently ongoing will be recorded at Screening and Baseline (Appendix A). Surgery and radiation history will include date and type.

A menstrual history will be obtained for all female patients at Screening.

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 start of study to treat Cushing syndrome, diabetes, and/or hypertension.

6.3 Safety Assessments

Safety parameters, including physical examination findings, vital signs, ECG results, pregnancy tests, clinical laboratory test results (hematology and chemistry), thyroid function tests, lipid profile, AEs, and concomitant medications, will be assessed at the time points specified Appendix A. In patients with pituitary Cushing syndrome, a pituitary magnetic resonance imaging (MRI) scan will be performed to evaluate tumor size. During the RW phase, clinical laboratory test results (hematology and chemistry), thyroid functions tests, and lipid profiles will remain blinded.

In the event study visits are shortened due to the COVID-19 pandemic, safety assessments should be prioritized.

6.3.1 Physical Examination

A complete physical examination, including evaluation of general appearance, head, eyes, ears, nose, and throat, as well as dermatologic, cardiovascular, respiratory, gastrointestinal, extremities/musculoskeletal, and neurologic body systems, will be performed (Appendix A).

Any clinically significant abnormalities observed during Screening should be reported in the patient's medical history; if observed any time after the first dose of study drug (Day 1) up to 28 days after the last dose of study drug, they will be considered treatment-emergent adverse events (TEAEs).

Height will only be measured at Screening (Appendix A).

6.3.2 Vital Signs

Vital signs, including BP, heart rate, respiratory rate, and oral body temperature, will be obtained at the time points specified in Appendix A. Blood pressure will be measured in both arms at Screening and the arm with the higher diastolic reading will be recorded and used for all subsequent measurements. Blood pressure and heart rate will be taken after the patient has rested in a sitting position for approximately 15 minutes and ≥30 minutes after smoking or caffeine intake. Automated BP machines can be used to standardize measurements.

Unscheduled assessments of vital signs can be performed as necessary.

In addition to the safety vital signs collected, a 24-hour ABPM will also be done by all patients at Screening and by patients with hypertension (Section 6.4.2) during treatment at the time points specified in Appendix A.

6.3.3 Electrocardiogram

Twelve-lead ECG tracings will be obtained in triplicate at Screening and in duplicate at other time points (2 hours ±30 minutes after study-drug dosing) as designated in Section 7 and in Appendix A. Patients should lie down for at least 10 minutes before each ECG evaluation. Electrocardiogram data will be submitted to a central reviewer; instructions will be provided in the study manual. A Sponsor-approved alternative option for ECGs (i.e., use of alternative locations for assessment) is permitted in the event of site closures due to the COVID-19 pandemic.

The Investigator or designee will indicate in the source documents 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.

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

6.3.4 Adverse Events

Details on definitions and reporting of AEs are provided in Section 8.

All AEs will be recorded from the time of signing of the ICF until 28 days after the last dose of study drug. Patients should be monitored for AEs throughout the study.

6.3.5 Clinical Laboratory Assessments

6.3.5.1 Laboratory Parameters

Fasting blood samples will be collected for the analysis of safety at the time points specified in Appendix A. Laboratory samples will be analyzed at 1 or more central laboratories; instructions will be provided in the laboratory manual.

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 whether any out-of-range laboratory values that emerge during the study are clinically significant. Any clinically significant laboratory value will be reported as an AE. 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.

During the RW phase, the results for all laboratory assessments will remain blinded. The unblinded Medical Monitor will review laboratory values and will notify the Investigator and study-site staff of any critical out-of-range laboratory values. To maintain the blind investigators should not repeat laboratory tests locally unless medically necessary.

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

Laboratory parameters, inclusive of efficacy, safety, PK, and pharmacodynamic (PD) parameters to be assessed are listed in Table 3.

Table 3 Clinical Laboratory Variables Evaluated During the Study

Hematology Red blood cell count Hemoglobin Hematocrit Mean corpuscular hemoglobin Mean corpuscular hemoglobin volume Mean corpuscular volume Platelet count Mean platelet volume Red blood cell distribution width White blood cell count Neutrophils (percent and absolute) Lymphocytes (percent and absolute) Monocytes (percent and absolute) Eosinophils (percent and absolute) Basophils (percent and absolute)	**Serum Chemistry** Sodium Potassium Calcium Chloride Phosphorus Magnesium Creatinine Creatine kinase Bilirubin (total and direct) Albumin Alkaline phosphatase Lactate dehydrogenase Aspartate aminotransferase Alanine aminotransferase Glucose 2-hour oGTT glucose 2-hour oGTT insulin HbA1c Blood urea nitrogen Uric acid Bicarbonate Total protein	**Glucocorticoid-Receptor Activity** FKBP5 and other potential biomarkers of GR activity
Pharmacokinetic Relacorilant		**Pregnancy** Serum/urine pregnancy test
Pharmacodynamic Urinary free cortisol Salivary cortisol Hypothalamic-pituitary-adrenal (HPA)-axis parameters: Plasma ACTH Serum DHEA-S Fasting serum cortisol	**Lipid Panel** Total cholesterol Low-density lipoprotein-cholesterol High-density lipoprotein-cholesterol Very low-density lipoprotein cholesterol Triglycerides	**Thyroid Function** Thyroid-stimulating hormone Total T3 Reflex Free T4 Reflex
		Sex Hormones Estradiol Testosterone (total and free) Sex-hormone–binding globulin Follicle-stimulating hormone Luteinizing hormone
		Biochemical Markers for Bone Remodeling Serum osteocalcin

ACTH, adrenocorticotropic hormone; DHEA-S, dehydroepiandrosterone sulfate; FKBP5, FK506 binding protein 5; HbA1c, glycated hemoglobin; oGTT, oral glucose tolerance test; T3, triiodothyronine; T4, thyroxine.

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 and GR activity biomarkers will also be provided.

6.3.5.2 Blood-Volume Summary

Blood samples will be used for analysis of safety laboratory, efficacy, PK, and pharmacodynamic parameters. The total volume of blood to be collected from each patient will be no more than 500.5 mL for his/her entire study participation.

6.3.6 Pituitary Magnetic Resonance Imaging Scan

In patients with pituitary Cushing syndrome, a pituitary MRI scan will be performed to evaluate tumor size (Appendix A). If the MRI cannot be performed with contrast (e.g., because of an allergy) it can be done without. The reason the MRI was performed without contrast should be documented. If the patient is contraindicated for MRI, a CT Scan may be performed instead. The reason the patient is contraindicated for MRI should be documented.

6.3.7 Pregnancy Test

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 undergo pregnancy tests. The Screening pregnancy test will be a blood test; all subsequent pregnancy tests will be urine tests, as specified in Appendix A.

6.4 Efficacy Assessments

All efficacy assessments will be performed at the time points specified in Appendix A.

6.4.1 Glucose Tolerance

A 2-hour oGTT will be used to assess the effect of relacorilant on glucose tolerance and insulin resistance (Matsuda Index and HOMA IR) following an 8-hour fast at the time points specified in Appendix A. 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 (Table 4). In general, patients 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. During the RW phase, the results to the study 2-hour oGTT will remain blinded.

Table 4 Time Window for Collection of 2-hour oGTT Blood Samples

Nominal Time	Reporting Standards
0.5, 1, 1.5, and 2 hours after the glucose drink	±10 minutes

In the event study visits are shortened due to the COVID-19 pandemic, the oGTT assessment should be prioritized.

6.4.2 Ambulatory Blood Pressure Monitoring (ABPM)

Ambulatory BP monitoring (ABPM) will be assessed. 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 (or under the condition of a Sponsor-approved alternative option in the event a patient is unable to come to the study site due to the COVID-19 pandemic). The patient should use the monitor during a time when a full 24-hour recording can be made. The patient should perform the ABPM under consistent conditions. ABPM will be performed at the time points specified in Appendix A. 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. ABPM should be initiated at the end of

the visit after collection of blood samples at each study visit. If more than 2 consecutive hours, or 5 hours over the entire period are missing then the data is considered missing and test should be repeated. During the RW phase, the results to the study 24-hour ABPM will remain blinded.

In the event study visits are shortened due to the COVID-19 pandemic, the ABPM assessment should be prioritized.

6.4.3 Glycated Hemoglobin (HbA1c)

Blood samples will be collected from patients to measure HbA1c, a glycoprotein whose concentration reflects the amount of glucose bound to hemoglobin, at the time points specified in Appendix A. During the RW phase, the HbA1c results will remain blinded.

In the event study visits are shortened due to the COVID-19 pandemic, the HbA1c assessment should be prioritized.

6.4.4 Body-Fat Composition (DXA Scan)

Change in the percent and absolute amounts of total body and regional fat and lean tissue (whole body, trunk, and leg) from Baseline (±6 weeks of the Baseline Visit) as measured by DXA scan (Shepherd et al. 2017) for all patients, at the time points specified in Appendix A.

6.4.5 Cushing Quality-of-Life Questionnaire

The Cushing QoL patient questionnaire, which evaluates the health-related QoL in patients with Cushing syndrome (Webb et al. 2008), will be administered to all patients at the time points specified in Appendix A. It comprises 12 questions, each with 5 possible answers. The total score ranges from 12–60. The Cushing QoL instrument addresses known problem areas associated with Cushing syndrome including trouble sleeping, wound healing/bruising, irritability/mood swings/anger, self-confidence, physical changes, ability to participate in activities, interactions with friends and family, memory issues, and future health concerns. Lower values reflect lower quality of life.

In the event a patient is unable to come to the study site due to the COVID-19 pandemic, the Cushing QoL patient questionnaire may be completed remotely and sent back to the site.

6.4.6 Body Weight and Waist Circumference

Body weight and waist circumference will be measured for all patients at the time points specified in Appendix A. Weight will be measured without overcoat and shoes and with only light clothing. Clinical sites will be provided with tape measures to ensure consistency of waist circumference measurements. Waist circumference measurements should be obtained to the nearest 0.5 cm (1/4 inch) following removal of clothing from the waistline. Detailed instructions for measurement of waist circumference will be provided in the study manual.

In the event study visits are shortened due to the COVID-19 pandemic, the waist circumference assessment should be prioritized if a DXA scan is unable to be completed.

6.4.7 Biochemical Markers of Bone Remodeling

Blood samples for analysis of serum osteocalcin will be obtained from all patients at the time points specified in Appendix A. During the RW phase, the serum osteocalcin results will remain blinded.

6.4.8 Beck Depression Inventory-II

The BDI-II, a 21-question self-report inventory that measures depression (Beck 1996), will be completed by all patients at the time points specified in Appendix A. Each answer is scored with values 0 to 3. The total score ranges from 0 to 63. Scores of 0 to 13 indicate minimal depression, 14 to 19; mild depression; 20 to 28; moderate depression; 29 to 63; severe depression.

6.4.9 Global Clinical Response

The DRB (see Section 5.10.1) will evaluate all patients for Global Clinical Response at the time points specified in Appendix A. The Global Clinical Response assessment (adapted from Katznelson et al. 2014) comprises items from 7 clinical categories:

1. Glucose: fasting blood glucose, 2-hour oGTT (Section 6.4.1), HbA1c (Section 6.4.3), change in diabetes medications
2. Blood pressure: systolic and diastolic blood pressure (Section 6.4.2), change in antihypertensive medications
3. Body composition: DXA Scan (Section 6.4.4), body weight and waist circumference (Section 6.4.6)
4. Clinical appearance (according to review of patient photographs): Cushingoid appearance and striae (Section 6.4.10)
5. Strength: sit-to-stand test (Section 6.4.11)
6. Psychiatric health/cognitive function: Beck Depression Inventory®-II (BDI-II) (Section 6.4.8), change in antidepressant medications, trail-making test
7. Quality of life: Cushing QoL score (Section 6.4.5)

Each of 3 members of the DRB will review the 7 categories of clinical parameters above to evaluate whether a patient's signs and symptoms of Cushing syndrome have changed, and will rate the patient's overall response based on the totality of signs and symptoms as +1 (improved), 0 (unchanged), or −1 (worsened) at every visit after Baseline. Each patient's final score will be the median of the 3 ratings.

During the OL phase, the change will be assessed with respect to Baseline, and during the RW Phase, it will be assessed with respect to the pre-randomization visit (Visit OL22).

6.4.10 Photography for Assessment of Cushingoid Features

Members of the DRB will review patient photographs to assess Cushingoid features (Colao et al. 2012) graphs at the time points specified in Appendix A. A digital camera will be supplied to take patient photographs. Detailed instructions for obtaining photographs will be provided in the study manual. A central vendor will collect patient photographs prior to assessment by the DRB. As a mitigation to the COVID-19 pandemic, patients will be allowed the option to perform self-capture for clinical photography, which will be completed on a mobile device. With this

method, it is possible that not all views may be captured. A central vendor will collect the self-captured photographs prior to the assessment by the DRB.

6.4.11 Sit-to-Stand

The sit-to-stand test will be performed at the time points specified in Appendix A. The sit-to-stand test evaluates the ability of patients to go from standing to sitting in a chair and then getting up again with/without the use of their arms or other aids. 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 5 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 (i.e., 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 5 times; start time is in the seated position and stop time is in the final standing position. The total time of the test is measured. 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.

6.4.12 Trail-Making Test

The trail-making test will be performed at the time points specified in Appendix A. The trail-making test is a neuropsychological test of visual attention and task switching that consists of 2 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 total time of the test is measured, with a maximum of 300 seconds.

6.4.13 Sex-Hormone Levels

Blood samples will be obtained from each patient at the time points specified in Appendix A for analysis of estradiol, total and free testosterone, sex-hormone–binding globulin, follicle-stimulating hormone, and luteinizing hormone. During the RW phase, the estradiol, total and free testosterone, sex-hormone–binding globulin, follicle-stimulating hormone, and luteinizing hormone results will remain blinded.

6.4.14 Menstrual Cycle Information

Menstrual cycle information (e.g., first day of last menstrual period, current pattern of menses, duration of vaginal bleed, compliance with hormonal birth control) will be recorded at the time points specified in Appendix A, along with any spotting occurrences, in premenopausal female patients.

6.4.15 Glucocorticoid Receptor Activity Biomarker Tests

A blood sample will be obtained from all patients for analysis of mRNA expression of glucocorticoid-modulated genes (including, among others, FKBP5) and proteins at the time

points specified in Appendix A. During the RW phase, the results for this assessment will remain blinded.

6.5 Pharmacokinetic Assessments

Intensive PK sampling will be conducted in all patients following an observed dose at Visit OL18 (Appendix A).

Intensive PK sampling will consist of a total of 5 samples collected at the following time points: predose (0 hour) and at 1, 2, 4, and 6 hours postdose (Table 5).

Instructions for the collection and handling of the samples will detailed in the laboratory manual.

PK sampling should be performed on the ongoing dose.

Table 5 Time Windows for Collection of Pharmacokinetic Samples

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

Refer to Section 9.5.7 for a description of PK analysis.

6.6 Pharmacodynamic Assessments

Samples for PD assessments will be collected from all patients at the time points specified in Appendix A. During the RW phase, the results for all PD assessments will remain blinded.

6.6.1 Fasting Serum Cortisol

Fasting serum cortisol samples will be obtained at the time points specified in Appendix A.

6.6.2 Urinary Free Cortisol

The 24-hour UFC with creatinine test will be collected by the patient at home at least 2 times during Screening and in duplicate at the other time points specified in Appendix A. A minimum of two 24-hour urinary samples are collected during Screening, at least 1 week apart. For Screening, the average of the results will serve as Baseline. During the Treatment Period, the 24-hour UFC sample should be collected in duplicate, at the patient's home, within 7 days prior to the next study visit. 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. Urinary free cortisol will be measured by tandem mass spectrometry.

6.6.3 Late-Night Salivary Cortisol

To assess late-night salivary cortisol, the salivary cortisol test will be performed by the patient at home twice on different nights during Screening and in duplicate at the other time points

specified in Appendix A. For Screening, the average of the results will serve as Baseline. The patient will be given supplies for the collection of saliva. Samples should be collected at bedtime. During the OL and RW phases, the late-night salivary cortisol sample should be collected in duplicate, at the patient's home, within 7 days prior to the next study visit. Patients should be instructed to avoid the chewing of licorice or tobacco 60 minutes prior to completing the test. Complete instructions will be provided to the patient.

6.6.4 Hypothalamic-Pituitary-Adrenal Axis Parameters

Blood samples will be obtained for analysis of plasma ACTH and dehydroepiandrosterone sulfate (DHEA-S) at the time points specified in Appendix A.

6.7 Appropriateness of the Measures

The assessments to be used in this study are standard for evaluation of patients with Cushing syndrome and are generally recognized as reliable, accurate, and relevant.

6.8 Blood Storage

A portion of the blood drawn predose at all visits (except the Screening Visit, Follow-up Visit, ET, and Unscheduled Visits) will be frozen and stored (for additional information on sample retention, see Section 11.4). These stored blood samples may be used by the Sponsor for retesting safety laboratory parameters, for measurement of study-drug and/or concomitant-drug levels in the blood, or for clinical laboratory testing to provide additional safety data. No human genetic testing will be performed without expressed consent of study patients.

7 STUDY ASSESSMENTS AND PROCEDURES BY STUDY VISIT

A Summary of Events (SOE) is provided in Appendix A. Most assessments are for all patients; a few are performed only in patients in a specific subgroup (i.e., the impaired glucose tolerance/diabetes subgroup or the uncontrolled hypertension subgroup).

In the event that a patient is unable to come to the clinic to participate in study-related visits or procedures, Sponsor-approved alternative options may be provided to the Investigator sites based on the needs and safety of patients. This may include the provision of study-drug dispensation and delivery outside of the clinic.

Any deviation from protocol procedures will be noted in the patient's clinical chart and eCRF. In addition, the Sponsor will be promptly notified of any protocol deviations. Though alternative methods for safety and study assessments (i.e., phone contact, virtual study visits, use of alternative locations for assessment, including local labs or imaging centers, etc.) are permitted due to the COVID-19 pandemic, any modified protocol-described processes should be recorded as protocol deviations.

7.1 Scheduled Visits

Patients requiring washout of a medication for Cushing syndrome must complete the Screening/Baseline 24-hour UFC tests, salivary cortisol tests, oGTTs, HbA1c, and 24-hour ABPM as described in Section 6.2.1.

The window for each study visit is relative to the Baseline or the Randomization Visit. The acceptable visit window is ±3 days for Visits OL2, OL6, and OL10 and ±7 days for all other visits (except when RW12 serves as the return visit following early discontinuation from the RW phase, in which case a 3-week visit window [2 weeks before the scheduled visit, 1 week after the scheduled visit] for RW12 is permitted). The Randomization visit (the first day of the RW phase) may occur up to 14 days after Visit OL22 to allow time to obtain the required test results to evaluate eligibility for the RW phase.

With regard to sequence of tests and acceptable time windows:

- Predose procedures must be completed before dosing and, where applicable, before breakfast.
- Dosing will take place at the scheduled time after completion of all predose procedures.
- At all visits beginning with OL2, study drug should be taken in the clinic during the visit and after initial blood draws.
- Pharmacokinetic sampling will take precedence over other procedures when more than 1 procedure is scheduled for the same time point relative to dosing. Acceptable time windows for PK samples at Visit OL18 are:

  Within 1 hour before dosing for the predose sample.
  ±10 minutes for the 1-, 2-, 4-, and 6-hour postdose samples.

- All clinical laboratory samples and predose PK samples will be collected when the patient is fasting (at least 4 hours).
- Ambulatory BP monitoring will be initiated in the clinic after all blood samples are obtained.

- Study-drug dosing should occur after the completion of the 2-hour oGTT test (except for OL18, when oGTT may take place after dosing for logistical issues due to serial PK sampling that would prolong patient stay).
- Acceptable time windows for oGTT samples are:

  ±10 minutes for the 0.5-, 1-, 1.5-, and 2-hour samples.

- Measurement of vital signs and ECG recordings will be avoided within 15 minutes after venipuncture or cannulation and, therefore, will normally be performed before blood sampling. Electrocardiogram recording should be performed 2 hours ±30 minutes after study-drug dosing.

The Investigator may repeat tests in the event of a technical failure and/or if additional observations or samples of blood are needed to monitor patient safety; these will not be considered protocol deviations.

The required procedures for each study visit are outlined in the study Schedule of Visits and Procedures in Appendix A.

7.1.1 Screening Visit (−42 to −1 day)

The purpose of the Screening visit/period is to ensure that appropriate patients are entered into the study and that they remain stable during the pretreatment period.

- Obtain written informed consent prior to performing any study procedures
- Review inclusion/exclusion criteria
- Complete medical history and review of medications
- Collect demographic and baseline disease characteristics information, including confirmation of medication washout
- Perform a complete physical examination, including height, weight, and waist circumference
- Measure vital signs
- Collect menstrual cycle information (premenopausal women only)
- Query for AEs
- Review concomitant medications
- Draw blood samples for laboratory tests
  - Serum pregnancy test (women of childbearing potential only).
  - Hematology and chemistry
  - 2-hour oGTT (after an 8-hour fast; must be performed within 2 weeks of Day 1 and used as Baseline)
  - HbA1c (must be collected within 2 weeks of Day 1 and will be used for Baseline)
  - HPA-axis parameters
  - GR-activity biomarker test
- DST (if warranted for study entry). A DST performed within 12 weeks before the ICF date will be accepted
- 24-hour UFC with creatinine (collected by the patient at home at least twice during Screening). For Screening, the average of the results will serve as “Baseline”

- Late-night salivary cortisol (collected by the patient at home at least twice on different nights during Screening). For Screening, the average of the results will serve as "Baseline"
- 12-lead ECG (obtained in triplicate during Screening)
- ABPM (24-hour) test will be assessed for all patients during Screening. For patients with hypertension, 24-hour ABPM must be completed within 2 weeks before Day 1 and used as Baseline
- Schedule next visit

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

7.1.2 Baseline Visit (B) (Day 1)

- Review inclusion/exclusion criteria
- Complete medical history and review of medications
- Collect demographic information and baseline disease characteristics
- Perform a complete physical examination, including weight and waist circumference
- Measure vital signs
- Collect menstrual-cycle information (premenopausal women only)
- Review and record AEs
- Review concomitant medications
- Draw blood samples for laboratory tests
  - Hematology and chemistry
  - Lipid panel (fasting)
  - Sex-hormone levels
  - GR-activity biomarker test
  - Serum osteocalcin
  - 2-hour oGTT (after an 8-hour fast and used as Baseline—unless performed within 2 weeks of Day 1; DM/IGT patients only)
  - HbA1c (used for Baseline—unless collected within 2 weeks of Day 1; DM/IGT patients only)
  - HPA-axis parameters
  - Thyroid function tests
- Collect urine sample for pregnancy test (women of childbearing potential only)
- Take photographs
- ABPM (24-hour) test (unless collected within 2 weeks of Day 1; hypertension patients only; initiated in clinic after all blood draws are obtained)
- DXA scan for body-fat composition (±6 weeks of the Baseline Visit)
- Sit-to-stand test
- Trail-making test
- Cushing QoL questionnaire
- Beck Depression Inventory
- Pituitary MRI scan (for patients with pituitary Cushing syndrome) (±6 weeks of the Baseline Visit)

- Dosing diary
- Study-drug dispensing and/or adherence
- Administration of the Day 1 dose of study drug
- 12-lead ECG (obtained in duplicate; 2 hours ±30 min after study-drug dosing)
- Schedule next visit

7.1.3 Open-Label Visit 2 (OL2) (±3 days)

- Perform a complete physical examination, including weight and waist circumference
- Measure vital signs
- Review and record AEs
- Review concomitant medications
- Draw blood samples for laboratory tests
  - Hematology and chemistry
- Collect urine sample for pregnancy test (women of childbearing potential only).
- Administration of the daily dose of study drug
- 12-lead ECG (obtained in duplicate; 2 hours ±30 min after study-drug dosing)
- ABPM (24-hour) test (hypertension patients only; initiated in clinic after all blood draws are obtained)
- Dosing diary
- Study-drug dispensing and/or adherence
- Schedule next visit

7.1.4 Open-Label Visit 6 (OL6) (±3 days)

- Perform a complete physical examination, including weight and waist circumference
- Measure vital signs
- Collect menstrual cycle information (premenopausal women only)
- Review and record AEs
- Review concomitant medications
- Draw blood samples for laboratory tests
  - Hematology and chemistry
  - GR-activity biomarker test
  - 2-hour oGTT (after an 8-hour fast; DM/IGT patients only)
  - HPA-axis parameters
- Take photographs
- Collect urine sample for pregnancy test (women of childbearing potential only)
- ABPM (24-hour) test (hypertension patients only; initiated in clinic after all blood draws are obtained)
- Late-night salivary cortisol (collected by the patient in duplicate at home within 7 days prior to the study visit)
- 24-hour UFC with creatinine (collected by the patient in duplicate at home within 7 days prior to the study visit)
- Sit-to-stand test

- Trail-making test
- Cushing QoL questionnaire
- Beck Depression Inventory
- Dosing diary
- Study-drug dispensing and/or adherence
- Administration of the daily dose of study drug
- 12-lead ECG (obtained in duplicate; 2 hours ±30 min after study-drug dosing)
- Schedule next visit

7.1.5 Open-Label Visit 10 (OL10) (±3 days)

- Perform a complete physical examination, including weight and waist circumference
- Measure vital signs
- Collect menstrual cycle information (premenopausal women only)
- Review and record AEs
- Review concomitant medications
- Draw blood samples for laboratory tests
  - Hematology and chemistry
  - GR-activity biomarker test
  - 2-hour oGTT (after an 8-hour fast; DM/IGT patients only)
  - HbA1c
  - HPA-axis parameters
- Take photographs
- Collect urine sample for pregnancy test (women of childbearing potential only).
- ABPM (24-hour) test (hypertension patients only; initiated in clinic after all blood draws are obtained)
- Late-night salivary cortisol (collected by the patient in duplicate at home within 7 days prior to the study visit)
- 24-hour UFC with creatinine (collected by the patient in duplicate at home within 7 days prior to the study visit)
- Sit-to-stand test
- Trail-making test
- Cushing QoL questionnaire
- Beck Depression Inventory
- Dosing diary
- Study-drug dispensing and/or adherence
- Administration of the daily dose of study drug
- 12-lead ECG (obtained in duplicate; 2 hours ±30 min after study-drug dosing)
- Schedule next visit.

7.1.6 Open-Label Visit 14 (OL14) (±7 days)

- Perform a complete physical examination, including weight and waist circumference
- Measure vital signs

- Collect menstrual cycle information (premenopausal women only)
- Review and record AEs
- Review concomitant medications
- Draw blood samples for laboratory tests
  - Hematology and chemistry
  - GR-activity biomarker test
  - 2-hour oGTT (after an 8-hour fast; DM/IGT patients only)
- Take photographs
- Collect urine sample for pregnancy test (women of childbearing potential only).
- ABPM (24 hour) test (hypertension patients only; initiated in clinic after all blood draws are obtained)
- Late-night salivary cortisol (collected by the patient in duplicate at home within 7 days prior to the study visit)
- 24-hour UFC with creatinine (collected by the patient in duplicate at home within 7 days prior to the study visit)
- Sit-to-stand test
- Trail-making test
- Cushing QoL questionnaire
- Beck Depression Inventory
- Dosing diary
- Study-drug dispensing and/or adherence
- Administration of the daily dose of study drug
- 12-lead ECG (obtained in duplicate; 2 hours ±30 min after study-drug dosing)
- Schedule next visit

7.1.7 Open-Label Visit 18 (OL18) (±7 days)

- Perform a complete physical examination, including weight and waist circumference
- Measure vital signs
- Collect menstrual cycle information (premenopausal women only)
- Review and record AEs
- Review concomitant medications
- Draw blood samples for laboratory tests
  - Hematology and chemistry
  - 2-hour oGTT (after an 8-hour fast; DM/IGT patients only)
  - Intensive PK sampling: predose and 1, 2, 4, and 6 hours postdose
- Take photographs
- Collect urine sample for pregnancy test (women of childbearing potential only).
- ABPM (24-hour) test (hypertension patients only; initiated in clinic after all blood draws are obtained)
- Sit-to-stand test
- Trail-making test
- Cushing QoL questionnaire

- Beck Depression Inventory
- Dosing diary
- Study-drug dispensing and/or adherence
- Administration of the daily dose of study drug
- Schedule next visit

7.1.8 Open-Label Visit 22 (OL22) (±7 days)

- Perform a complete physical examination, including weight and waist circumference.
- Measure vital signs
- Collect menstrual cycle information (premenopausal women only)
- Review and record AEs
- Review concomitant medications
- Draw blood samples for laboratory tests
  - Hematology and chemistry
  - Lipid panel (fasting)
  - Sex-hormone levels
  - GR-activity biomarker test
  - Serum osteocalcin
  - 2-hour oGTT (after an 8-hour fast; all patients)
  - HbA1c (all patients)
  - HPA-axis parameters
  - Thyroid function tests
- Take photographs
- Collect urine sample for pregnancy test (women of childbearing potential only).
- ABPM (24-hour) test (all patients; initiated in clinic after all blood draws are obtained)
- Late-night salivary cortisol (collected by the patient in duplicate at home within 7 days prior to the study visit)
- 24-hour UFC with creatinine (collected by the patient in duplicate at home within 7 days prior to the study visit)
- DXA scan for body-fat composition
- Sit-to-stand test
- Trail-making test
- Cushing QoL questionnaire
- Beck Depression Inventory
- Pituitary MRI scan (for patients with pituitary Cushing syndrome)
- Dosing diary
- Study-drug dispensing and/or adherence
- Administration of the daily dose of study drug
- 12-lead ECG (obtained in duplicate; 2 hours ±30 min after study-drug dosing)
- Schedule next visit

7.1.9 Randomization Visit (R) (+14 days)

- Review response criteria
- Perform a complete physical examination, including weight and waist circumference
- Measure vital signs
- Review and record AEs
- Review concomitant medications
- Collect urine sample for pregnancy test (women of childbearing potential only)
- Dosing diary
- Randomization
- Study-drug dispensing and/or adherence
- Administration of the daily dose of study drug
- Schedule next visit

7.1.10 Randomized-Withdrawal Visit 4 (RW4) (±7 days)

- Perform a complete physical examination, including weight and waist circumference
- Measure vital signs
- Collect menstrual cycle information (premenopausal women only)
- Review and record AEs
- Review concomitant medications
- Draw blood samples for laboratory tests
  - Hematology and chemistry
  - 2-hour oGTT (after an 8-hour fast; DM/IGT patients only)
- Collect urine sample for pregnancy test (women of childbearing potential only).
- ABPM (24-hour) test (hypertension patients only; initiated in clinic after all blood draws are obtained)
- Sit-to-stand test
- Trail-making test
- Cushing QoL questionnaire
- Beck Depression Inventory
- Dosing diary
- Study-drug dispensing and/or adherence
- Administration of the daily dose of study drug
- Schedule next visit

7.1.11 Randomized-Withdrawal Visit 8 (RW8) (±7 days)

- Perform a complete physical examination, including weight and waist circumference
- Measure vital signs
- Collect menstrual cycle information (premenopausal women only)
- Review and record AEs
- Review concomitant medications
- Draw blood samples for laboratory tests
  - Hematology and chemistry

  - 2-hour oGTT (after an 8-hour fast; DM/IGT patients only)
- Collect urine sample for pregnancy test (women of childbearing potential only).
- ABPM (24-hour) test (hypertension patients only; initiated in clinic after all blood draws are obtained)
- Sit-to-stand test
- Trail-making test
- Cushing QoL questionnaire
- Beck Depression Inventory
- Dosing diary
- Study-drug dispensing and/or adherence
- Administration of the daily dose of study drug
- Schedule next visit

7.1.12 Randomized-Withdrawal Visit 12 (RW12) (±7 days)

If a patient discontinues early from the RW phase, the patient will be instructed to return for Visit RW12 per the patient's original dosing schedule. If this visit is the return visit following early discontinuation from the RW phase, a 3-week visit window (2 weeks before the scheduled visit, 1 week after the scheduled visit) is permitted.

- Perform a complete physical examination, including weight and waist circumference
- Measure vital signs
- Collect menstrual cycle information (premenopausal women only)
- Review and record AEs
- Review concomitant medications
- Draw blood samples for laboratory tests
  - Hematology and chemistry
  - Lipid panel (fasting)
  - Sex-hormone levels
  - GR-activity biomarker test
  - Serum osteocalcin
  - 2-hour oGTT (after an 8-hour fast; all patients)
  - HbA1c (all patients)
  - HPA-axis parameters
  - Thyroid function tests
- Take photographs
- Collect urine sample for pregnancy test (women of childbearing potential only).
- ABPM (24-hour) test (completed by the patient at home within 7 days prior to the study visit; all patients)
- Late-night salivary cortisol (collected by the patient in duplicate at home within 7 days prior to the study visit)
- 24-hour UFC with creatinine (collected by the patient in duplicate at home within 7 days prior to the study visit)
- DXA scan for body-fat composition

- Sit-to-stand test
- Trail-making test
- Cushing QoL questionnaire
- Beck Depression Inventory
- Dosing diary
- Study-drug dispensing and/or adherence (patients will remain on study drug up to 1 week post the RW12 visit until it has been confirmed that all results for efficacy and safety assessments are available and no repeat assessments are required)
- 12-lead ECG (obtained in duplicate; 2 hours ±30 min after study-drug dosing)
- Schedule next visit

7.1.13 Early-Termination Visit (±7 days)

If a patient discontinues prior to Visit OL22, the following assessments will be performed at the time of discontinuation or soon thereafter:

- Perform a complete physical examination, including weight and waist circumference
- Measure vital signs
- Collect menstrual cycle information (premenopausal women only)
- Review and record AEs
- Review concomitant medications
- Draw blood samples for laboratory tests
  - Hematology and chemistry
  - Lipid panel (fasting)
  - Sex-hormone levels
  - GR-activity biomarker test
  - Serum osteocalcin
  - 2-hour oGTT (after an 8-hour fast; all patients)
  - HbA1c (all patients)
  - HPA-axis parameters
  - Thyroid function tests
- Take photographs
- Collect urine sample for pregnancy test (women of childbearing potential only).
- ABPM (24-hour) test (all patients; initiated in clinic after all blood draws are obtained)
- Late-night salivary cortisol (collected by the patient in duplicate at home within 7 days prior to the study visit)
- 24-hour UFC with creatinine (collected by the patient in duplicate at home within 7 days prior to the study visit)
- 12-lead ECG (obtained in duplicate)
- DXA scan for body-fat composition (should not be repeated if completed within 8 weeks prior to ET Visit)
- Sit-to-stand test
- Trail-making test
- Cushing QoL questionnaire

- Beck Depression Inventory
- Pituitary MRI Scan (for patients with pituitary Cushing syndrome; should not be repeated if completed within 3 months of ET Visit)
- Dosing diary
- Study-drug adherence.

7.1.14 Follow-up Visit (±7 days)

For patients who do not enroll in the extension study, the post-treatment Follow-Up visit will occur 28 days after the last dose of study drug.

- Perform a complete physical examination, including weight and waist circumference.
- Measure vital signs.
- Review and record AEs
- Review concomitant medications
- Draw blood samples for laboratory tests
  - Hematology and chemistry
- Collect urine sample for pregnancy test (women of childbearing potential only).
- 12-lead ECG (obtained in duplicate).

For patients who discontinue the study prior to the RW12 visit during the Randomized Withdrawal phase of the study and return for the RW12 visit, the follow up visit will be waived if the RW12 visit occurs at least 28 days after the last dose of administration of study drug.

7.2 Unscheduled Visits

As appropriate, assessments deemed clinically necessary by the Investigator may be conducted at unscheduled visits.

8 SAFETY EVENT DOCUMENTATION AND REPORTING

8.1 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.

8.2 Monitoring Safety Data During Study

Safety results collected during the study (e.g., AEs, laboratory test results, physical findings) will be monitored on an ongoing basis by the Medical Monitor and Investigator. In addition, an Independent Data Monitoring Committee (IDMC) will be established to conduct periodic reviews of data to ensure the safety of patients (Section 5.10.2). During the RW phase, 2-hour oGTT and ABPM results will be reviewed by an unblinded Medical Monitor to monitor patient safety.

8.3 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 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.

8.4 Definition of a Serious Adverse Event

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

- Results in death (i.e., the AE caused or led to the fatality).
- Is life-threatening (i.e., 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 (i.e., hospitalizations for scheduled treatments and elective medical/surgical procedures are not SAEs by this criterion).
- Results in persistent or significant disability/incapacity (i.e., 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 (i.e., 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 (i.e., 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).

8.5 Clinical Significance

The Investigator (or medically qualified designee) is responsible for determining whether an AE is clinically significant for the patient. Clinical significance will be documented in the patient's medical records with the AE information.

8.6 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.

8.7 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. Illnesses present before the patient signs the ICF are considered pre-existing conditions and are documented on the medical history eCRF. Preexisting conditions that worsen during the study are entered on the AE eCRF. Adverse events that occur after start of study drug 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 and do not need to be reported to Corcept, unless the event meets the definition of serious (see Section 8.4) and the relationship to the study drug is possibly or probably related (see Section 8.8.2). In such cases, these posttreatment SAEs need to be reported per the process in Section 8.9.

All AEs for enrolled patients 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 (Section 8.8.1), (4) relationship to the study drug (Section 8.8.2), (5) "serious" criteria, if applicable (Section 8.4), 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 that are possibly or probably related to the study drug and unexpected (not reported in the Investigator's Brochure or greater severity or frequency than that described in the Investigator's Brochure) must be reported to the governing IRB/Independent Ethics Committee (IEC)/Health Authorities, as required.

8.8 Adverse-Event Classification

8.8.1 Intensity 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 Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 5.0 (NCI-CTCAE 2017). For events not listed in the CTCAE, the definitions from the CTCAE provided in Table 6 should be used to evaluate the grade of severity of the AE.

Table 6 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 (e.g., 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 (e.g., 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

CTCAE; Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute
Source: NCI-CTCAE 2017

8.8.2 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 7. The Investigator's assessment of causality must be provided for all AEs (serious and nonserious).

Table 7 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, or for which it is temporally implausible to be related to use of the study drug. 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, e.g., 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, e.g., concomitant drug(s) or concurrent disease(s).

8.9 Procedures for Reporting a Serious Adverse Event

Any SAE occurring from the time of signing of the ICF and for at least 28 days after the last dose of study drug *must be reported immediately (latest 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 (e.g., autopsy reports and terminal medical reports).

Serious AE reporting details are provided below, as well as in the study manual.

Reporting Contact Details:

clinicalsafety@corcept.com

8.10 Adverse Event Follow-up

All AEs considered to be possibly or probably related (Section 8.8.2) to the study drug and all SAEs 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.

8.11 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to Corcept during the study and within 28 days of the last dose of study drug. The patient will be followed to determine the outcome of the pregnancy, and the outcome will be reported.

8.11.1 Maternal Exposure

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

If a pregnancy occurs during the study or within 28 days of the last dose of study drug, 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 by completing the Pregnancy report form and submitting via email to clinicalsafety@corcept.com.

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.

8.11.2 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 if possible be followed and documented. 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; the male patient should not be asked to provide this information. A consent form specific to this situation must be used. The outcome of any conception occurring from the date of the first dose until 28 days after dosing should be followed and documented.

8.12 Treatment of Overdose

There is currently no experience with overdose of relacorilant. For monitoring symptoms of excessive GR antagonism, refer to Section 5.3.1. If clinically significant GR antagonism is suspected, dexamethasone may be administered.

8.13 Emergency Sponsor Contact

In a medical emergency (i.e., 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 listed on the cover page.

9 STATISTICAL METHODS

9.1 Analysis Populations

The ITT-RW population will include all patients who were randomized in the double-blind RW phase and received at least one dose of study drug. The mITT-RW population will include all patients in the ITT-RW population with at least one post-randomization efficacy assessment for the primary efficacy endpoint (ABPM). The ITT-RW population will be used for the analysis of the primary endpoint in the RW Phase.

The per-protocol analysis population (PP-RW) will include all patients in the mITT-RW population who completed the study according to protocol specifications without a major deviation. Protocol deviations resulting in exclusion from the PP population will be identified in the Statistical Analysis Plan (SAP). The determination of the PP analysis population will be finalized prior to database lock. Patients in the PP population who complete the RW phase without a major deviation will be used in sensitivity analyses of the primary endpoint and the secondary endpoints in the RW phase. The mITT-RW and PP-RW populations will be used for supportive efficacy analyses of all endpoints in the RW Phase.

The ITT-OL population will include all enrolled patients who received at least one dose of study drug. The mITT-OL population will include all patients in the ITT-OL population with at least one post-baseline efficacy assessment for efficacy endpoints. The per-protocol analysis (PP-OL) population will include all patients in the mITT-OL population who had no major protocol deviations that might impact the validity of the primary efficacy analysis. The ITT-OL, mITT-OL, and PP-OL populations will be used for supportive efficacy analyses of all endpoints in the OL Phase.

Analyses of glycemic control response measures will be performed on all patients in the ITT population with DM/IGT regardless of whether they have hypertension at Baseline. Analyses of hypertension response measures will be performed on all patients in the ITT population with hypertension, regardless of whether they have DM/IGT at Baseline.

The Safety Population will consist of all enrolled patients who received at least 1 dose of study drug. It will be used for all safety analyses.

9.2 General Statistical 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 before database lock.

All continuous variables will be summarized using descriptive statistics (number of patients, means, percentiles, standard deviations) and confidence intervals (CIs) for values measured at each visit, as well as changes from Baseline. For categorical variables, counts, percentages, and their 95% CIs will be presented for each visit.

Predose measurements on Day 1 will be considered the Baseline values for the OL phase (Baseline). If a Day 1 predose value is not available, the Screening measurement may be used as the Baseline value. For patients who were randomized in the RW phase, the measurements

collected at the visit prior to RW phase will be considered as the Baseline for the RW phase (RW Baseline).

9.3 Hypothesis Testing

All statistical hypotheses will be tested at a 2-sided 0.05 significance level unless otherwise specified. No adjustments for multiplicity will be made for secondary and exploratory endpoints.

9.4 Sample-Size Calculation

Approximately 162 patients are planned to enroll into a 6-month OL phase of the study to ensure the randomization of approximately 46 patients with hypertension into the subsequent 3-month, placebo-controlled RW phase.

This calculation assumes that enrolled patients will consist of approximately 25% with DM/IGT only, 25% with hypertension only, and 50% with both DM/IGT and hypertension at Screening. Attainment of the randomization targets within the hypertension subgroup in the RW phase further assumes that 75% of patients that present with hypertension only randomize to the RW phase and 20% of patients that present with both comorbidities (DM/IGT and hypertension) respond to hypertension criteria at Visit OL22 (hypertension only or DM/IGT and hypertension as described in Section 3.1) and randomize to the RW phase. These assumptions will result in approximately 30 patients from the hypertension subgroup, and 16 patients from the DM/IGT and hypertension subgroup randomizing to the RW phase; thus, a total of approximately 46 patients meeting response criteria will be randomized into the hypertension subgroup of the ITT-RW analysis population.

Study enrollment will be monitored to ensure attainment of randomization targets. To maintain sufficient power to detect treatment difference, the number of patients enrolled in the OL phase may be adjusted to ensure a sufficient number of patients meeting response criteria to uncontrolled hypertension are randomized in the RW phase. Enrollment of patients may continue based on enrollment target projections.

Forty-six patients with hypertension (23 per treatment group) will ensure at least 90% power to detect the difference between placebo and treatment arms in loss of response, assuming a loss of response in 25% of patients in the treatment arm and 75% in the placebo arm. These calculations are based on a Fisher's exact test of proportions at the alpha=0.05 two-sided significance level.

In summary, randomization of patients in the RW phase will continue to ensure enrollment of 46 patients meeting response criteria within the hypertension subgroup. This sample size will provide sufficient power to detect the target differences in the primary endpoint for the hypertension subgroup.

9.5 Analysis Plan

9.5.1 Patient Disposition

The numbers of patients who were screened and who participated in the OL and RW phases along with the reasons for withdrawal in each phase will be summarized.

9.5.2 Demographic and Baseline Data

Demographics and baseline characteristics will be summarized for the Safety Population, ITT-OL, and ITT-RW populations. The summaries will include frequencies and percentages for categorical variables, and mean, standard deviation, median, minimum, and maximum for continuous variables.

These summaries will include patient medical history, including the diagnosis, etiology, and treatment history of Cushing syndrome.

9.5.3 Prior and Concomitant Medications

A list of all medications for diabetes, hypertension, or Cushing-syndrome–related comorbidities used at Baseline and each study visit will be generated.

9.5.4 Analysis of Efficacy Endpoints

9.5.4.1 Analysis of the Primary Efficacy Endpoint

For the hypertension subgroup of the ITT-RW population, the primary analysis will be a responder analysis and the odds ratio for loss of response in hypertension control will be reported, as well as the percentage of patients with loss of response and 95% CI (using Clopper-Pearson method). The loss of response with respect to hypertension will be compared between treatment and placebo arms at Visit RW12 using a logistic regression model with 2 independent variables (treatment arm and stratification factor). In the hypertension subgroup, this stratification factor identifies patients with or without DM/IGT.

In the hypertension subgroup, loss of response in the RW phase is defined as: use of rescue medication for hypertension after randomization but before Visit RW12, discontinuation of treatment before Visit RW12, or increase in SBP/DBP of >5 mmHg documented after randomization. This will be considered the primary analysis for the endpoint loss of response with respect to hypertension at Visit RW12 in the hypertension subgroup of the ITT-RW population.

A sensitivity analysis of the primary endpoint by region will be done. Details will be described in the SAP. Additional sensitivity analyses may be pre-specified in the SAP.

9.5.4.2 Approach to Missing Data Analysis

All efforts will be made to prevent missing data. In the hypertension subgroup of the ITT-RW population, patients that discontinue treatment prior to Visit RW12, use rescue medication prior to Visit RW12, or for whom SBP/DBP measurements were not collected at Visit RW12, and therefore have missing data at Visit RW12 will be considered as non-responders in the primary analysis for loss of response in hypertension control.

Imputation of missing data at Visit RW12 for the secondary continuous endpoints (i.e., SBP, DBP) related to assessment of hypertension control will be performed based on data from retrieved dropouts, with similar baseline characteristics, within the same treatment arm. For patients who use rescue medication for hypertension before Visit RW12, a placebo-based mean imputation method will be used to impute the Visit RW12 value. If fewer than 10 retrieved

dropouts are available, then the main analysis will use a wash-out multiple imputation method instead of the retrieved dropout approach.

In patients in the DM/IGT subgroup, imputation of missing data at Visit RW12 for the secondary endpoint of change in $AUC_{glucose}$ from Visit OL22 to Visit RW12 will be performed depending on whether or not patient takes rescue medication. For patients who do not use rescue medication for DM/IGT before Visit RW12 (regardless if they discontinue treatment), all values for $AUC_{glucose}$ up to the Visit RW12, will be used in the analysis (including values from retrieved dropouts). Patients who do not take rescue medication for whom $AUC_{glucose}$ at Visit RW12 is missing will have data imputed based on data from retrieved dropouts, with similar baseline characteristics, within the same treatment arm. For patients who use rescue medication for DM/IGT before Visit RW12, the values measured after the use of rescue medication are considered irrelevant to the clinical question of interest. In this case, a placebo-based mean imputation method will be used.

The guidance on *The Prevention and Treatment of Missing Data in Clinical Trials* (National Research Council 2010) will be followed when these methods are applied.

9.5.4.3 Multiplicity Adjustment for Secondary Efficacy Endpoints

No adjustment for multiplicity will be made for secondary and exploratory endpoints.

9.5.4.4 Analysis of the Secondary Efficacy Endpoints in the RW Phase

For continuous endpoints in the RW phase of the study, the analysis will be performed using a linear MMRM model. Restricted maximum likelihood (REML) estimation will be used. The MMRM model will include Visit OL22 value (for the respective endpoint) as a covariate; treatment, visit, treatment by visit interaction, and stratification factor as fixed effects; and patients within treatment groups as random effects. An unstructured covariance structure will be used to model within-patient error, and the Kenward-Roger approximation will be used to model denominator degrees of freedom. This model is used after imputation of missing data at Visit RW12, using the retrieved drop-out approach. If fewer than 10 retrieved dropouts are available for the endpoint, then the main analysis will use a wash-out multiple imputation method instead of the retrieved dropout approach.

The analysis for each of the endpoints will determine whether there is a difference between treatment groups in terms of change from Randomization to Visit RW12. This will be accomplished by using appropriate linear contrasts of the parameters in the MMRM model described above. Additional details will be described in the SAP.

For all endpoints described as proportions in the RW phase, the point estimate and the 2-sided 95% CI will be calculated.

Sensitivity analyses will be pre-specified in the SAP.

9.5.4.5 Analyses of Exploratory Efficacy Endpoints

The Exploratory Endpoints listed in Section 3.6.3 will be analyzed using methods similar to the analyses of secondary endpoints described in Section 9.5.4.4 and will be detailed further in the SAP.

9.5.5 Safety Analyses

Safety variables will be analyzed for the Safety Population, defined as all patients who received at least 1 dose of study drug.

TEAEs will be summarized separately in the following four categories: Overall TEAEs; TEAEs that start prior to Randomization; TEAEs that start after randomization through the end of RW phase, summarized by treatment group; and TEAEs that start during the follow-up period summarized by treatment group. TEAEs for patients who were not randomized will be summarized separately. Serious AEs and TEAEs that lead to study drug withdrawal or withdrawal from the study will be listed by patient.

TEAEs will be summarized by study period and treatment, as applicable, and displayed using the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term, as well as by intensity and relationship to the study drug. Serious AEs and treatment-emergent AEs that lead to study drug withdrawal or withdrawal from the study will be listed by patient.

Clinical laboratory test results (chemistry and hematology), vital sign measurements, and ECG interval results will be summarized as changes over the OL phase and RW phase by parameter and visit using descriptive statistics. Changes in the laboratory results during the Follow-up period will be summarized separately. Shift tables will describe changes from Baseline in clinical laboratory values.

9.5.6 Pharmacodynamic Analysis

Analysis of PD endpoints, which include changes from Baseline to Visit OL22/ET in fasting serum cortisol, UFC, late-night salivary cortisol, and plasma ACTH levels, will be described in the SAP finalized before database lock.

9.5.7 Pharmacokinetic Analysis

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

10 ETHICAL AND LEGAL CONSIDERATIONS

10.1 Compliance with IRB/IEC Regulations

This study is to be conducted in accordance with IRB regulations (US 21 Code of Federal Regulations [CFR] Part 56.103), IEC regulations, or applicable local regulations. The protocol, ICFs, recruitment materials, and all patient materials will be submitted to the IRB/IEC for review and approval. Approval of both the protocol and the ICF must be obtained before any patient is enrolled, and the Investigator must submit written approval to the Sponsor, before enrolling any patient. The Investigator is responsible for informing the IRB/IEC of any amendment to the protocol in accordance with local requirements. The protocol must be re-approved by the IRB or IEC on receipt of amendments and annually, as local regulations require.

All changes to the ICF must be approved by the IRB/IEC; a determination will be made regarding whether previously consented patients need to be re-consented.

Corcept is to be notified immediately if the responsible IRB/IEC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB/IEC correspondence with the Investigator should be provided to Corcept.

Progress reports and notifications of SAEs will be provided to the IRB or IEC according to local regulations and guidelines.

10.2 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 applicable country and local regulations.

10.3 Protection of Human Patients

10.3.1 Compliance with Informed-Consent Regulations

Written informed consent is to be obtained from each patient before enrollment into the study.

The Principal Investigator(s) at each study site 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 ICF 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.

10.3.2 Patient Confidentiality

To maintain patient privacy, all study reports and communications will identify the patient by 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 as required by applicable laws and regulations.

10.3.3 Patient Privacy

The Investigator or designee must explain to each patient, before enrollment into the study, that for evaluation of study results, the patient's protected health information obtained during the study may be shared with the Sponsor, regulatory agencies, and IRBs/IECs/Research Ethics Board. It is the Investigator's (or designee's) responsibility to obtain written permission to use protected health information per country-specific regulations from each patient. If permission to use protected health information is withdrawn, it is the Investigator's responsibility to obtain a written request, to ensure that no further data are collected from the patient and that the patient is removed from the study.

Written authorization is to be obtained from each patient before enrollment into the study in accordance with the applicable privacy requirements.

10.3.4 Data Protection

Corcept, as Data Controller, ensures that all processing activities involving personal data performed in the scope of this study are compliant with, but not limited to, the requirements set by EU General Data Protection Regulation (GDPR 679/2016), its subsequent amendments and any additional national laws on Data Protection, recommendations and guidelines as applicable.

To comply with the applicable rules on the protection of personal data, specifically regarding the implementation of the organizational and technical arrangements aiming to avoid unauthorized access, disclosure, dissemination, alteration or loss of information and processed personal data, Corcept has implemented and maintains the following measures:

- Restriction and monitoring of physical access to the offices and information processing facilities to employees, personnel and approved visitors;
- Appropriate and restricted user access relevant to the function and type of activity performed in relation to the clinical trial;
- Effective pseudonymization of personal data in compliance with EDPB Recommendations 01/2020 (v2.0 adopted 18 June 2021);
- Encryption of personal data, where appropriate;
- Ability to ensure the ongoing confidentiality, integrity, availability and resilience of processing systems and services;

- Network, application and database security by means of firewalls and antivirus/anti-malware; ensuring detection of malware purposed for unauthorized deletion, blocking, copying of information, disabling security measures and response to such attacks;
- Means to restore the availability and access to personal information in a timely manner in the event of a physical or technical incident;
- Logging of security events/incidents in information systems;
- Procedures that cover reporting, analysis, monitoring and resolution of security incidents;
- Ensuring that information systems, computers and software involved in the performance of the services provided in the study are backed up;
- A process for regularly testing, assessing and evaluating the effectiveness of technical and organizational measures for ensuring the security of the processing;
- Procedures to capture in a timely manner if a personal data breach has occurred;
- Procedures and practices for destruction of paper documents containing personal data;
- Business continuity procedures ensuring that Corcept can continue to provide services through operational interruption.

All locations, personnel and information systems that are used to perform services for the study will be covered;

Corcept will ensure technical and organizational security measures described above, are regularly reviewed and updated to take into account any evolution on technological developments.

Corcept may apply additional specific statutory requirements, where applicable in the national laws, and will implement the necessary security measures even if they are not expressly listed above.

Besides the already above-mentioned technical and organizational measures, Corcept, by means of internal measures and imposed contractual clauses to the selected vendors and partners (in their role of processors), ensures the confidentiality of records and personal data of subjects.

With exception of the activities in the scope of the on-site monitoring, inspections, or audits , the name of the patient will neither be asked for, nor recorded by the Corcept. An identification number will be allocated to each patient registered in the study. This number will identify the patient and will be included on all case report forms and corresponding material and data associated with the patient.

Monitors acting on behalf of the Corcept will have access to fully identifiable information only in the scope of the on-site monitoring visits, and only for the source data verification mandatory under clinical trial framework, including the ICH-GCP obligations applicable to the conduct of the study. Staff involved in the performance of this task is bound by any additional stricter confidentiality clauses imposed upon them, as compared to other staff members.

Corcept has put in place a functional process of reporting of any data breach occurring at Corcept or its vendor’s and partner’s (in their role of processor) facilities and premises. In case of the occurrence of any data breach, Corcept will immediately apply relevant measures to mitigate the risks to data subjects as appropriate in relation to the specific context of the data breach, taking into account its source, underlying intentions, possibilities of recovery, etc. Any data breach presenting risks to the rights and freedoms of data subjects will be reported to the relevant

supervisory data protection authority within 72 hours of Corcept becoming aware of the data breach. In addition, in case of occurrence of a high-risk breach, data subjects will be informed by the Corcept (via clinical-study site).

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Quality Management

As part of quality management based on a risk-based approach per ICH E6(R2): risk reduction activities may be incorporated in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to standard operating procedures, and training in processes and procedures.

Predefined quality tolerance limits should be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact subject safety or reliability of trial results. Detection of deviations from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed.

Study sites, the study database, and study documentation will be monitored regularly and may be subject to a quality assurance audit during the study by the IRB/IEC and/or the Sponsor or its designee. In addition, inspections may be conducted by regulatory agencies at their discretion.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks will be run on the database. Any missing data or data anomalies will be communicated to the study site(s) for clarification/resolution.

Following written SOPs, the study-specific monitoring plan, the monitors will verify that the clinical study is conducted, data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices, Good Manufacturing Practices).

Upon request, the investigational site will provide direct access and allow the Sponsor (or its representative including monitors and/or auditors), IRB/IEC and regulatory authorities to review and inspect all trial-related sites, drug storage area, study-drug stock, drug accountability records, patient charts, source documents, and other records related to study conduct.

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

11.2 Study Monitoring

The Sponsor, or designee, will be responsible for the monitoring of the study. Study monitors will contact and visit the Investigators at regular intervals throughout the study to answer study questions, and to systematically and independently examine all study-related activities, verify adherence to the protocol, and assess the completeness, consistency, and accuracy of the data.

Monitoring may include, but is not limited to:

- Reviewing eCRFs for accuracy and completeness.
- Assessing compliance with the protocol and adherence to regulatory and GCP requirements.
- Verifying that the site maintains an adequate supply of study drugs, any necessary supplies, and that appropriate storage conditions are maintained.

Monitoring visits will be conducted according to the ICH Guideline for GCP and all applicable country and local regulations and guidance.

By agreeing to participate in this research study, the Investigators agree to co-operate with the study monitor to ensure that any problems detected during the monitoring visits are promptly resolved.

Monitoring methods, responsibilities, and requirements will be outlined in the study monitoring plan.

11.3 Documentation

11.3.1 Source Documents

Source documents provide all original records of clinical findings, observations, or other information from a clinical trial necessary for the reconstruction and evaluation of the trial (e.g., a patient's medical records, hospital charts, clinic charts, the Investigator's patient study files, results of diagnostic tests, including x-rays, laboratory tests and ECGs). All source data should be attributable, legible, contemporaneous, original, accurate, and completed. Changes to source data should be traceable (i.e., dated and initialed), should not obscure the original entry, and should be explained, if necessary.

Investigators must retain all original source documents. The Sponsor or its designee will notify Investigators in writing when the trial-related records are no longer needed.

11.3.2 Case Report Forms

The Investigator must generate and maintain complete, adequate, accurate, reliable, and legible records in a timely manner to enable full documentation of study conduct. All data entered into CRFs (paper or electronic) must be substantiated by and consistent with a source document.

Discrepancies between CRFs and their respective source documents should be explained. All changes in eCRF data entry at the study site will be performed by designated site personnel and will be in the clinical database audit trail. In the event paper CRFs are utilized, any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry.

All changes in CRF data entry at the study site will be performed by designated site personnel.

11.3.3 Retention of Essential Study Documents

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified.

Study essential documents, which include the patient identification code list (i.e., patient names and corresponding study numbers), should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period, however, if required by local regulations.

No records will be destroyed without the written consent of the Sponsor, if applicable. If the Investigator can no longer maintain the records, it is the responsibility of the Investigator to contact the Sponsor. These documents may be transferred to another responsible party, acceptable to the Sponsor, who agrees to abide by the retention policies. Written notification of transfer must be submitted to the Sponsor. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

11.3.4 Sample Collection, Preparation, and Shipping

Instructions for collection, preparation, and shipping of all laboratory samples will be provided in the Study Laboratory Manual.

11.4 Long-Term Retention of Biological Samples

All biological samples will be retained by the Sponsor or designee under the original informed consent of the patient and the IRB/IEC approval. Samples will be held for a period up to 15 years after completion of the clinical study report. The Sponsor or its designee may store the patient's sample(s) longer if required to address regulatory agency questions; in this event, the patient's sample(s) will be destroyed after all questions are adequately answered.

An individual patient can choose to withdraw consent to have their samples used for future research at any time without affecting their participation in the study or their care by the health provider. After receipt of a request for sample destruction, that patient's sample(s) will then no longer be used for future research purposes beyond the current study, and their sample(s) will be destroyed. However, if there are ongoing regulatory questions, the patient's sample(s) will be destroyed after all questions are adequately answered.

The long-term retention samples will be coded to allow de-identification according to applicable regulatory guidelines. It is the responsibility of the trial site to ensure that samples are appropriately labeled in accordance with trial procedures to comply with all applicable laws.

Biological samples collected from participants as part of this trial will be transported, stored, accessed, and processed in accordance with all applicable laws relating to the use and storage of human tissue for research purposes.

Such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act and the 2006 Human Tissue (Scotland) Act.

Samples may be subject, but not limited to European Directives 2002/58/EC, the General Data Protection Regulation 2016/679, and any legislation and/or regulation implementing or made pursuant to them, or which amends, replaces, re-enacts, or consolidates any of them, and all other applicable laws relating to processing of personal data and privacy that may exist in any relevant jurisdiction.

11.5 Clinical Supplies

11.5.1 Inventory, Reconciliation, Return, and Disposition of Clinical Supplies

All study drug and related materials should be stored, inventoried, reconciled, and destroyed or returned according to applicable state and federal regulations/government health authorities and study procedures. Storage of study drug is described in Table 1.

11.5.2 Clinical-Supply Inventory

Each clinical site is required to complete and maintain a detailed inventory for all study drug. The study drug is to be used in accordance with the protocol by patients who are under the direct supervision of an Investigator. The study drug must be dispensed only by an appropriately designated and qualified person to patients in the study.

Unused study drug must be kept in a secure location for accountability and reconciliation by the study monitor. The Investigator or their designee must provide an explanation for any destroyed or missing study drug or study materials.

The Investigator or their designee is responsible for maintaining accurate records (including dates and quantities) of study drug(s) received, patients to whom study drug is dispensed (patient-by-patient dose-specific accounting), and study drug lost or accidentally or deliberately destroyed. The Investigator or their designee must retain all unused or expired study supplies until the study monitor (on-site clinical research associate) has confirmed the accountability data and Sponsor has approved return or destruction.

11.5.3 Return or Destruction of Study Drug and/or Supplies

At the end of the study, after final drug-inventory reconciliation by the study monitor, the study site will either return study drug and/or supplies to the Sponsor or designee, or destroy all unused study drug and/or supplies, including empty containers, according to institutional policy.

11.5.4 Study Drug Destroyed by the Site

Unused/undispensed study drug and/or supplies may be destroyed on site, per the site's SOPs, but only after Sponsor has granted approval for drug destruction. The study monitor must account for all study drug in a formal reconciliation process, before study drug destruction. All study drug destroyed on site must be documented.

Any destruction of study drug on site must be documented. Documentation must be provided to the Sponsor and retained in the Investigator study files.

11.5.5 Study Drug Returned to Sponsor for Destruction

If a site is unable to destroy unused/undispensed study drug and/or supplies appropriately, the site can request return of study drug and/or supplies to the Sponsor or designee.

The return of study drug and/or supplies must be accounted for on a Study Drug Return Form provided by the Sponsor or designee.

11.5.6 Drug Accountability

It is the responsibility of the Investigator to maintain drug accountability at the study site and ensure that a current record of study drug disposition is maintained. It is the responsibility of the Investigator to ensure that the study drug is used only in accordance with the approved protocol. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient dispensing records, and returned, lost, or accidentally or deliberately destroyed study product.

Dispensing records will document quantities received from the Sponsor (or its designee) and quantities dispensed to patients, including lot number, date dispensed, patient identifier number, patient initials, the initials of the person dispensing the drug, quantities of drug returned by the patients and disposal/return of returned study drug.

11.6 Post-Trial Care

There is provision of continued access to study drug by way of a roll-over/extension study (Section 3.2.3).

11.7 Protocol Noncompliance

A protocol deviation is any noncompliance with requirements in the clinical-trial protocol, GCP, or the manual of procedures (MOP) requirements. The noncompliance may be on the part of the patient, the Investigator, or the study-site staff. As a result of deviations, corrective actions consistent with ICH E6(R2) may be implemented.

Prospective approval of deviations from the inclusion and exclusion criteria, known as protocol waivers or exemptions, is not permitted. Changes to the conduct of the protocol may not be made, except to address an immediate risk to the patient, unless the change has been submitted to the regulatory authorities for review and the change has been approved by the IRB/IEC.

Sponsor clinical-study staff and contractors may acknowledge, but not approve, protocol deviations reported by a site that have happened or are planned to happen.

Any significant protocol deviations affecting patient eligibility and/or safety or data integrity must be submitted to the IRB/IEC and regulatory authorities, as applicable, prior to implementation.

After the protocol is approved by the Sponsor and by IRB/IEC, any change that might affect the approval of the IRB/IEC must be documented in the form of a protocol amendment. The amended protocol must be approved by the IRB/IEC and annually, as local regulations require.

11.8 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.

11.9 Publication and Disclosure Policy

Corcept, as the Sponsor, has a proprietary interest in this study.

No individual publications will be allowed before publication of the multicenter results, except as agreed with the Sponsor. The Investigator agrees to submit all manuscripts or abstracts to the Sponsor for review before submission to the publisher.

The Sponsor will comply with the requirements for publication of study results and determination of authorship in accordance with standard editorial and ethical practice and with the International Committee of Medical Journal Editors (ICMJE) requirements.

11.10 Electronic Systems

All electronic systems, including clinical study sites, clinical operations, data management, biostatistics, safety, and CRO systems, etc., used to collect, manage, and storage study data should be validated and in compliance with 21 CFR Part 11 and EU Annex 11 guideline. The validation documentation should be made available at all times during inspection or Sponsor audits. Any modification to the validated system should be documented via a quality change control process and justified for their intended use.

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13 APPENDICES

Appendix A: Schedule of Events

Table 8 Schedule of Visits and Procedures

Study Procedure	Screening [a]	Baseline	Open-Label Phase Weeks 1 to 22						Random-ization	Randomized-Withdrawal Phase (Weeks 1 to 12)			Early Term-ination	Follow-up [b]
Visit Name	—	B	OL2	OL6	OL10	OL14	OL18	OL22	R	RW4	RW8	RW12	ET	—
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Visit Window (d)	−42 to −1	—	±3d	±3d	±3d	±7d	±7d	±7d	+14	±7d	±7d	±7d[aa]	±7d	±7d
Informed consent	X	-	-	-	-	-	-	-	-	-	-	-	-	-
Inclusion/exclusion criteria	X	X	-	-	-	-	-	-	-	-	-	-	-	-
Response criteria	-	-	-	-	-	-	-	-	X	-	-	-	-	-
Medical and medication history [c]	X	X	-	-	-	-	-	-	-	-	-	-	-	-
Demographics/baseline disease characteristics	X	X	-	-	-	-	-	-	-	-	-	-	-	-
Physical examination [d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Waist circumference	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs [e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events [f]	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
Photographs [g]	-	X	-	X	X	X	X	X	-	-	-	X	X	-
12-Lead ECG [h]	X	X	X	X	X	X	-	X	-	-	-	X	X	X
Pregnancy test (women only) [i]	X (s)	X (u)	X (u)	X (u)	X (u)	X (u)	X (u)	X (u)	X (u)	X (u)	X (u)	X (u)	X (u)	X (u)
Chemistry [j], Hematology [k]	X	X	X	X	X	X	X	X	-	X	X	X	X	X
Lipid panel (fasting) [l]	-	X	-	-	-	-	-	X	-	-	-	X	X	-

Study Procedure	**Screening [a]**	**Baseline**	**Open-Label Phase Weeks 1 to 22**						**Random-ization**	**Randomized-Withdrawal Phase (Weeks 1 to 12)**			**Early Term-ination**	**Follow-up [b]**
Visit Name	**—**	**B**	**OL2**	**OL6**	**OL10**	**OL14**	**OL18**	**OL22**	**R**	**RW4**	**RW8**	**RW12**	**ET**	**—**
Sex-hormone levels [m]	-	**X**	-	-	-	-	-	**X**	-	-	-	**X**	**X**	-
GR activity biomarker tests	**X**	**X**	-	**X**	**X**	**X**	-	**X**	-	-	-	**X**	**X**	-
Serum osteocalcin [n]	-	**X**	-	-	-	-	-	**X**	-	-	-	**X**	**X**	-
2-hour oGTT [o]	**X**	**X[bb]**	-	**X**	**X**	**X**	**X**	**X**	-	**X**	**X**	**X**	**X**	-
HbA1c [p]	**X**	**X[bb]**	-	-	**X**	-	-	**X**	-	-	-	**X**	**X**	-
HPA-axis parameters [q]	**X**	**X**	-	**X**	**X**	-	-	**X**	-	-	-	**X**	**X**	-
Thyroid function tests [r]	-	**X**	-	-	-	-	-	**X**	-	-	-	**X**	**X**	-
Intensive PK sampling [s]	-	-	-	-	-	-	**X** [s]	-	-	-	-	-	-	-
24-hour UFC with creatinine [t]	**X**	-	-	**X**	**X**	**X**	-	**X**	-	-	-	**X**	**X**	-
DST [u]	**X**	-	-	-	-	-	-	-	-	-	-	-	-	-
Late-night salivary cortisol [t]	**X**	-	-	**X**	**X**	**X**	-	**X**	-	-	-	**X**	**X**	-
Menstrual cycle information [v]	**X**	**X**	-	**X**	**X**	**X**	**X**	**X**	-	**X**	**X**	**X**	**X**	-
DXA scan for body-fat composition	-	**X** [w]	-	-	-	-	-	**X**	-	-	-	**X**	**X** [w]	-
ABPM (24-hour) test [x]	**X**	**X[bb]**	**X**	**X**	**X**	**X**	**X**	**X**	-	**X**	**X**	**X**	**X**	-
Sit-to-stand test	-	**X**	-	**X**	**X**	**X**	**X**	**X**	-	**X**	**X**	**X**	**X**	-
Trail-making test	-	**X**	-	**X**	**X**	**X**	**X**	**X**	-	**X**	**X**	**X**	**X**	-
Cushing QoL questionnaire	-	**X**	-	**X**	**X**	**X**	**X**	**X**	-	**X**	**X**	**X**	**X**	-
Beck Depression Inventory	-	**X**	-	**X**	**X**	**X**	**X**	**X**	-	**X**	**X**	**X**	**X**	-
Pituitary MRI scan	-	**X** [y]	-	-	-	-	-	**X**	-	-	-	-	**X** [y]	-
Dosing diary	-	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	-
Study-drug dispensing and/or adherence [z]	-	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X[cc]**	**X**	-

ABPM, ambulatory blood pressure monitoring; BP, blood pressure; DM/IGT, diabetes mellitus/impaired glucose tolerance; DRB, Data Review Board; DST, dexamethasone suppression test; DXA, dual-energy x-ray absorptiometry; ECG, electrocardiogram; ET, early termination; GR, glucocorticoid receptor; HbA1c, glycated hemoglobin; HPA, hypothalamic-pituitary-adrenal; MRI, magnetic resonance imaging; oGTT, oral glucose tolerance test; OL, open-label; PK, pharmacokinetics, QoL, quality-of-life; RW, randomized withdrawal; (s), serum; (u), urine; UFC, urinary free cortisol.

a Medications used in the treatment of Cushing syndrome are prohibited and require washout (as applicable) during Screening if the intervals specified in Exclusion Criteria 12 and 13 fit within the Screening window. Patients requiring washout of a medication for Cushing syndrome must complete the Screening/Baseline HbA1c tests, oGTTs, and 24-hour ABPM tests after washout and within 2 weeks before Day 1 dosing; 24-hour UFC tests and salivary cortisol tests must be completed after washout.
Screening assessments performed during the 6-week screening window can be used as Baseline data and assessments do not need to be repeated unless otherwise noted.

b For patients who do not enroll in an extension study, the Follow-up visit will occur 28 days after the last dose of study drug. For patients who discontinue the study prior to the RW12 visit during the Randomized Withdrawal phase of the study and return for the RW12 visit, the follow up visit will be waived if the RW12 visit occurs at least 28 days after the last dose of administration of study drug.

c Medication history for medications taken to treat Cushing syndrome, hypertension, or diabetes within 3 months before start of study.

d Height is measured at Screening only. At all visits, Investigators will assess the general physical appearance of patients during the examination.

e Vital signs: BP, heart rate, respiratory rate, oral body temperature.

f Adverse events will be collected after the informed consent form is signed. Events ongoing at study entry are considered medical history.

g Members of the DRB will review patient photographs to assess Cushingoid features.

h ECGs will be obtained in triplicate at Screening and in duplicate at other study visits. ECGs will be obtained 2 hours ±30 minutes after study-drug dosing.

i Pregnancy tests: for women of childbearing potential: (s)=serum pregnancy test at Screening; (u)=urine pregnancy test at other time points.

j Chemistry parameters: full chemistry profile that includes albumin, alkaline phosphatase, ALT, AST, bicarbonate, 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. Results will remain blinded during the RW phase.

k Hematology parameters: a complete blood count and differential. Results will remain blinded during the RW phase.

l Lipid panel: total cholesterol, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, very low-density lipoprotein-cholesterol, and triglycerides. Results will remain blinded during the RW phase.

m Sex hormones: estradiol, total and free testosterone, sex-hormone–binding globulin, follicle-stimulating hormone, and luteinizing hormone. Results will remain blinded during the RW phase.

n Results will remain blinded during the RW phase.

o oGTT: the 2-hour oGTT will be performed on all patients during Screening. A 2-hour oGTT will be performed only in patients with DM/IGT except Visit OL22, Visit RW12, and ET Visit (if applicable), when a 2-hour oGTT will be performed for all patients. During the 2-hour oGTT, blood samples for plasma glucose and insulin are collected before the glucose drink and 0.5, 1, 1.5, and 2 hours after the glucose drink. Screening visit oGTT glucose results must be collected within 2 weeks of Day 1 and will be used for Baseline. Results will remain blinded during the RW phase. In patients randomized to the DM/IGT subgroup, oGTT assessments will continue as planned until Visit RW12.

p HbA1c: Screening visit HbA1c results must be collected within 2 weeks of Day 1 and will be used for Baseline. During treatment with study drug, HbA1c will be performed in all patients during Screening, Visit OL10, Visit OL22, Visit RW12, and ET Visit (if applicable) and only in patients with DM/IGT during other indicated visits. Unless collected within 2 weeks of Day 1, HbA1c will be performed at Baseline (in DM/IGT patients only). Results will remain blinded during the RW phase.

q HPA-axis: plasma ACTH, fasting serum cortisol, and DHEA-S. Results will remain blinded during the RW phase.

r Thyroid function tests: free T4 Reflex, Total T3 Reflex, thyroid-stimulating hormone. Results will remain blinded during the RW phase.

s PK at OL18: blood samples will be collected in all patients following the observed dose at Visit OL18, predose (0 hour) and at 1, 2, 4, and 6 hours postdose.

t UFC and salivary cortisol: 24-hour UFC and salivary cortisol test samples will be collected by the patient at home at least twice during Screening. A minimum of two 24-hour urinary samples are collected during Screening, at least 1 week apart. The average of the results will serve as Baseline. During the treatment with study drug, the 24-hour UFC and late-night salivary cortisol samples should be collected in duplicate, at the patient's home, within 7 days prior to the next study visit. Results will remain blinded during the RW phase.

u DST: 1-mg overnight or 2-mg 48-hour test may be performed during Screening or within 12 weeks before signing the informed consent, if necessary.

v Menstrual cycle information: obtain only from premenopausal female patients.

w DXA scan: Baseline assessment may be performed ±6 weeks prior to Baseline Visit; scan should not be repeated if completed within 8 weeks before the ET Visit.

x ABPM: The 24-hour ABPM will be assessed for all patients during Screening. For patients with uncontrolled hypertension, a 24-hour ABPM test must be performed within the 2 weeks prior to Day 1; this result will be used as Baseline. ABPM measurements during the study will be performed only for patients with hypertension except for Visit OL22, Visit RW12, and ET Visit (if applicable) when ABPM measurements will be assessed for all patients. Results will remain blinded during the RW phase. In patients randomized to the hypertension subgroup, ABPM assessments will continue as planned until Visit RW12.

y Pituitary MRI: Baseline assessment may be performed ±6 weeks prior to Baseline Visit; scan does not need to be repeated if completed within 3 months of ET Visit.

z At ET visit, only study adherence needs to be performed; no study drug should be dispensed. Administration of study drug is the last procedure at applicable visits, other than at visit OL18, when it should be administered prior to blood draws for PK assessment.

aa If this visit is the return visit following early discontinuation from the RW phase, a 3-week visit window (2 weeks before the scheduled visit, 1 week after the scheduled visit) is permitted.

bb oGTT (in DM/IGT patients only), HbA1c (in DM/IGT patients only), and ABPM (in hypertension patients only) will only be performed at Baseline if the prior assessment was not performed within 2 weeks.

cc Patients will remain on study drug up to 1 week post RW12 visit until it has been confirmed that all results for efficacy and safety assessments are available and no repeat assessments are required.

Appendix B: Summary of Changes

Significant changes in Amendment 7 of the protocol dated 17 May 2024 compared with Amendment 6 dated 22 April 2024 are summarized below with additional details in Table 9; deleted text is shown as a ~~strikethrough~~ and new text is shown in **bold**.

Minor editorial or stylistic changes made for consistency are not summarized and may not be shown in the redline version of the amendment (e.g., punctuation, spelling, abbreviations). Table of Contents, lists of tables or figures are updated without redline.

Significant revisions to the protocol include the following:

- Secondary and exploratory endpoints and their analysis methods were revised

Table 9 Summary of Changes in Protocol CORT125134-455 Amendment 6

Section	Summary of Change	Revisions
Global changes	Updated version and date of the protocol.	~~Amendment 6~~**Amendment 7** ~~22 April 2024~~**17 May 2024**
Synopsis	Updated text in synopsis to align with changes in the protocol body.	--
3.6.2 Secondary Efficacy Endpoints in the Randomized-Withdrawal Phase	Added secondary endpoint; no longer distinguishing between key secondary and other secondary endpoints.	~~Key Secondary Endpoint~~ -- ~~Other Secondary Endpoints~~ -- • **In patients with DM/IGT, the mean change in HbA1c from Visit OL22 to Visit RW12, as compared between relacorilant and placebo.**
3.6.3 Exploratory Efficacy Endpoints in the Randomized Withdrawal Phase	Added exploratory endpoint.	• **In all patients randomized in the RW phase, proportion of patients with a loss of response with respect to hypertension or hyperglycemia from Visit OL22 to Visit RW12 based on 24-hour ABPM and $AUC_{glucose}$ as compared between relacorilant and placebo arms, where loss of response is defined as follows:** – **In patients with hypertension only at Baseline OL:** ▪ **In patients who met only the SBP response criterion, an increase in SBP ≥5 mm Hg.** ▪ **In patients who met only the DBP response criterion, an increase in DBP by ≥5 mm Hg.** ▪ **In patients who met both the SBP and DBP response criteria, an increase in either SBP or DBP by ≥5 mm Hg.** ▪ **Any increase or modification in antihypertensive medication due to worsening hypertension.** ▪ **Patients discontinue treatment in RW phase for any reason.** – **In patients with DM/IGT only at Baseline OL:** ▪ **A ≥10% increase from Baseline RW in $AUC_{glucose}$ from Visit OL22 to Visit RW12.** ▪ **Use of rescue medication (initiation or increase in diabetes medication due to worsening of hyperglycemic control).** ▪ **Treatment discontinuation for any reason in RW phase.** ▪ **Patients with missing RW12 $AUC_{glucose}$ values.** • **In patients with hypertension and DM/IGT at Baseline OL, a loss of response will be defined as a loss of response with respect to either**

Section	Summary of Change	Revisions
		hypertension or hyperglycemic control (AUC-based) from Visit OL22 to Visit RW12, irrespective of which response criteria (hypertension or DM/IGT) they met to enter the RW phase.
3.6.4 Exploratory Efficacy Endpoints in the Open-Label Phase	Exploratory endpoints added.	Endpoints Summarized with Proportions -- • **In patients with DM/IGT, the proportion of patients with ≥25% decrease in AUCglucose from Baseline to Visit OL22/ET.** • **In patients with DM/IGT, the proportion of patients with ≥0.5% decrease in HbA1c from Baseline to Visit OL22/ET.**
9.3 Hypothesis Testing	Revised analysis methods.	~~In order to ensure experiment-wise Type I error control, the secondary endpoints will be tested using a hierarchical testing approach at a 2-sided alpha level of 0.05. If the null hypothesis is rejected for the primary endpoint, secondary endpoints will be sequentially tested following the gatekeeping hierarchy specified in the SAP.~~ No adjustments for multiplicity will be made for **secondary and** exploratory endpoints.
9.5.4.1 Analysis of the Primary Efficacy Endpoint	Revised analysis methods.	~~As a sensitivity analysis, patients for whom loss of response in hypertension control at Visit RW12 is missing because ABPM measurements are not available (non-retrieved dropouts), will have data imputed based on data from retrieved dropouts, with similar baseline characteristics, within the same treatment arm.~~
9.5.4.2 Approach to Missing Data Analysis	Clarified analysis methods.	**If fewer than 10 retrieved dropouts are available, then the main analysis will use a wash-out multiple imputation method instead of the retrieved dropout approach.**
9.5.4.3 Multiplicity Adjustment for Secondary Efficacy Endpoints	Clarified analysis methods.	~~Details regarding adjustment for multiplicity across primary and secondary endpoints will be provided in the SAP.~~ **No adjustment for multiplicity will be made for secondary and exploratory endpoints.**
9.5.4.4 Analysis of the Secondary Efficacy Endpoints in the RW Phase	Revised analysis methods based on no longer differentiating between key secondary and other secondary endpoints; clarified analysis methods.	~~The loss of response (AUC-based) with respect to hyperglycemic control will be compared between treatment and placebo arms at Visit RW12 using a logistic regression model with 2 independent variables (treatment arm and stratification factor). In the DM/IGT subgroup, this stratification factor identifies patients with or without hypertension.~~ ~~For all endpoints described as proportions in the RW phase, the point estimate and the 2-sided 95% CI will be calculated.~~ -- **This model is used after imputation of missing data at Visit RW12, using the retrieved drop-out approach. If fewer than 10 retrieved dropouts are available for the endpoint, then the main analysis will use a wash-out multiple imputation method instead of the retrieved dropout approach.** --

Section	Summary of Change	Revisions
		For all endpoints described as proportions in the RW phase, the point estimate and the 2 sided 95% CI will be calculated. **Sensitivity analyses will be pre-specified in the SAP.**
12 References	Reference list updated to remove citations no longer referenced.	--