Title: Glucocorticoid Receptor Antagonism in the Treatment of Hypercortisolism in Patients with Cortisol-Secreting Adrenal Adenomas or Hyperplasia (GRADIENT): A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Relacorilant

NCT Number: NCT04308590

Date: 11 October 2024

CLINICAL STUDY PROTOCOL CORT125134-456

Title	**Glucocorticoid Receptor Antagonism in the Treatment of Hypercortisolism in Patients with Cortisol-Secreting Adrenal Adenomas or Hyperplasia (GRADIENT): A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Relacorilant**
EudraCT Number	2019-004956-12
Study drug	Relacorilant (CORT125134)
Medical Monitor (blinded)	[redacted]
Sponsor	Corcept Therapeutics Incorporated 101 Redwood Shores Parkway Redwood City, California 94065 USA (650) 327-3270
Version	Amendment 3
Date	11 October 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, 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 Hypercortisolism in Patients with Cortisol-Secreting Adrenal Adenomas or Hyperplasia (GRADIENT): A Phase 3, Randomized, Double-Blind, Placebo-Controlled 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]
Chief Development Officer
Corcept Therapeutics Incorporated

SYNOPSIS

Title	Glucocorticoid Receptor Antagonism in the Treatment of Hypercortisolism in Patients with Cortisol-Secreting Adrenal Adenomas or Hyperplasia (GRADIENT): A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Relacorilant
Study Number	CORT125134-456
Name of Active Ingredient	relacorilant
Name of Sponsor	Corcept Therapeutics Incorporated
Phase of Development	3
Study Centers	Approximately 60 sites (North America and other international sites)
Sample Size	Approximately 130 patients

Study Objectives

Primary Objectives

- To assess the efficacy of relacorilant for the treatment of hypercortisolism in patients with cortisol-secreting adrenal adenomas or hyperplasia, based on blood pressure (BP) control at Week 22 compared with placebo
- To assess the safety of relacorilant for the treatment of hypercortisolism

Secondary Objectives

- To assess changes in the cortisol excess-related comorbidities (e.g., body weight and glycemic control) in patients with hypercortisolism due to cortisol-secreting adrenal adenomas/hyperplasia

Exploratory Objectives

- To explore changes in cortisol excess-related comorbidities including assessments of glucose, insulin resistance indices, coagulation markers, GR activity biomarkers, HPA axis, and bone turnover markers, depression and quality of life questionaries in patients with cortisol-secreting adrenal adenomas or hyperplasia
- To assess the pharmacokinetics of relacorilant in patients with hypercortisolism due to cortisol-secreting adrenal adenomas/hyperplasia

Study Population

This study includes patients with cortisol-secreting adrenal adenomas or hyperplasia associated with DM/IGT and/or uncontrolled systolic hypertension.

Number of Patients Planned

Approximately 130 patients are planned to be randomized.

Duration of Patient Participation

Screening: Up to 6 weeks

Randomized, double-blind, placebo-controlled: 22 weeks

Follow-up: Within 28 days after the last dose of study drug

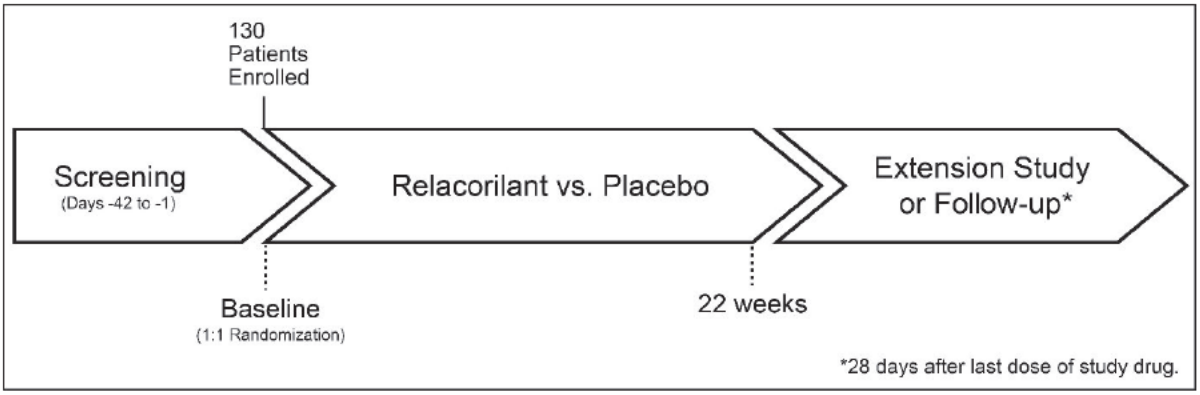
Total participation: Up to 32 weeks

Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled study to assess the efficacy, and safety of relacorilant to treat hypercortisolism in patients with cortisol-secreting adrenal adenoma or hyperplasia associated with DM/IGT and/or uncontrolled systolic hypertension.

Two subgroups—DM/IGT and hypertension—will be analyzed.

Figure S1 CORT125134-456 Study Design



Study Phases

Screening Phase

Up to 6 weeks to determine study eligibility.

Randomized, Double-Blind, Placebo-Controlled Phase (Baseline to Week 22)

Baseline is defined as Day 1 of the double-blind, placebo-controlled study.

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 hyperglycemia and/or hypertension. The starting dose at Baseline will be 100 mg relacorilant or matching placebo 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 titrations after Week 18 are not permitted. Dose escalation will be performed based on tolerability assessed by the unblinded Medical Monitor considering the following factors (only in patients whose current dose is well tolerated).

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

- is ≥140 mg/dL or
- is <140 mg/dL and has not decreased by ≥30 mg/dL from Baseline

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

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

In patients with both DM/IGT and systolic hypertension:

- The 2-hour glucose of the oGTT:
- is ≥140 mg/dL or
- is <140 mg/dL and has not decreased by ≥30 mg/dL from Baseline

OR

The average 24-hour systolic BP (based on ABPM):

is ≥130 mm Hg or

is <130 mm Hg and has not decreased by ≥5 mm Hg from Baseline

Dose escalation may be held if the patient cannot safely tolerate escalation to the next dose.

Every effort should be made to administer study drug on the planned dose and schedule. However, if in the opinion of the Investigator a relacorilant dose is not tolerated, a dose interruption or dose reduction is permitted. Re-escalation after a dose reduction is permitted, with the approval of the Medical Monitor.

Patient Disposition

Patient Study Completion

Patients who complete 22 weeks of the double-blind, placebo-controlled phase and return for the follow-up visit 28 days after the last dose of study drug will be considered to have completed the study. The follow-up visit will serve as the last study visit.

Patients who complete 22 weeks of the double-blind, placebo-controlled phase, and enter an extension study without interruption will also be considered to have completed the study; in that case the follow-up visit will not be required, and Week 22 will serve as the last study visit.

Treatment Continuation

Patients who complete the study will be permitted to continue relacorilant treatment in an extension study provided that they have at least 80% adherence with scheduled dosing (by capsule counts).

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 the Week 22 visit.

Patients who complete the Week 22 visit and do not wish to enter an extension safety study will be instructed to discontinue study drug. Patients should not discontinue study drug before all the Week 22 assessments are performed and the unblinded medical monitors confirm all the data required for the analysis of the primary endpoint have been collected and reported. The follow-up visit will be conducted 28 days after the last dose of study drug and will serve as the last study visit.

Early Patient Discontinuation or Withdrawal

If a patient discontinues early from the study, the patient will complete an early termination (ET) visit at the time of last dose of study drug or within 2 weeks. The patient will be instructed to return to the site for the Week 22 visit per their original dosing schedule, and for the follow-up visit 28 days after the last dose of study drug. Depending on the timing of the patient's discontinuation, the visits may happen out of sequence, and either visit may serve as the patient's last study visit.

Study Endpoints

Primary Endpoints

1. **In patients with systolic hypertension**, the mean change in 24-hour average SBP based on 24-hour ABPM, from Baseline to Week 22 as compared between relacorilant and placebo arms.
2. **In all patients**, assessment of safety based on TEAEs.

Secondary Endpoints (from Baseline to Week 22/ET, compared between relacorilant and placebo)

Endpoints for Hypertension

1. In patients with systolic hypertension at Baseline, mean change in average DBP and HR (based on 24-hour ABPM).
2. In patients with systolic hypertension at Baseline, mean change in daytime average SBP, DBP, and HR (based on 24-hour ABPM).
3. In patients with systolic hypertension at Baseline, mean change in nighttime average SBP, DBP, and HR (based on 24-hour ABPM).
4. In patients with systolic hypertension at Baseline, proportion of patients with any dose increase in antihypertensive medications due to worsening hypertension.
5. In patients with systolic hypertension at Baseline, proportion of patients with a reduction in 24-hour average SBP by 5 mm Hg (based on 24-hour ABPM).
6. In patients with systolic hypertension at Baseline, proportion of patients with any dose decrease in antihypertensive medication due to improved blood pressure.
7. In patients with systolic hypertension at Baseline, proportion of patients with normalization of the average SBP (<130 mm Hg, based on 24-hour ABPM).

Endpoints for Hyperglycemia

1. In patients with DM/IGT at Baseline, the mean change in $AUC_{glucose}$, from Baseline to Week 22 as compared between relacorilant and placebo arms.
2. In patients with DM (HbA1c at Baseline ≥6.5%), the mean change in HbA1c.
3. In patients with DM/IGT (HbA1c at Baseline ≥5.7%), the mean change in HbA1c.
4. Proportion of patients with HbA1c ≥6.5% at Baseline who achieved HbA1c <6.5%.
5. In patients with DM at Baseline, proportion of patients who achieved 2-hour oGTT glucose <140 mg/dL.
6. In patients with IGT at Baseline, proportion of patients who achieved 2-hour oGTT glucose <140 mg/dL.
7. In patients with DM/IGT at Baseline, proportion of patients with any dose decrease of diabetes medication due to improved glucose control.
8. In patients with DM/IGT at Baseline, proportion of patients with any dose increase of diabetes medications due to worsening hyperglycemia.
9. In patients with DM/IGT in the ITT population, the proportion of patients who achieved decrease of $AUC_{glucose}$ of ≥25%, ≥10%, ≥5% and any decrease from Baseline to Week 22.
10. In patients with DM/IGT in the ITT population, the mean change in 2-hour oGTT 2-hour timepoint from Baseline to Week 22.
11. In patients with DM/IGT in the ITT population, the mean change in 2-hour oGTT predrink timepoint from Baseline to Week 22.

Other Secondary Endpoint

1. In all patients, the mean change in body weight and waist circumference.

Exploratory Efficacy Endpoints

The mean change from Baseline to Week 22/ET in serum osteocalcin; in trabecular bone score, bone mineral density, and body composition from DXA scans; the Beck Depression Inventory®-II (BDI-II) score; sit-to-stand test score; trail making test scores; coagulation markers (Factor VIII, von Willebrand factor, protein S, protein C, TAT, platelets, and PTT); biomarkers related to GR activity (such as FKBP5); DHEA-S concentrations; ACTH concentrations; lipids (total cholesterol, LDL cholesterol, triglycerides, and very-low-density lipoprotein cholesterol); HPA-axis; difference between morning and late-night salivary cortisol; $AUC_{glucose}$; fasting glucose in patients with DM; insulin resistance indices and hyperglucagonemia ($AUC_{insulin}$, Matsuda Index, homeostatic model assessment of insulin resistance [HOMA IR], and at selected visits $AUC_{glucagon}$); and Cushing Quality-of-Life (Cushing QoL) score.

Intensive pharmacokinetic blood sampling will be conducted in all patients at the Week 18 visit. The plasma concentrations of relacorilant and/or its metabolites will be examined.

Inclusion Criteria

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

1. Male or female, 18 to 80 years of age, inclusive.
2. Lack of cortisol suppression (>1.8 µg/dL serum cortisol with adequate dexamethasone levels) on either 1-mg overnight or 2-mg 48-hour DST during Screening.
3. Suppressed or low (≤15 pg/mL) early-morning ACTH levels on at least 2 occasions during Screening.
4. A radiologically confirmed benign adrenal lesion (single adenoma, multiple adenomas, hyperplasia [≥3 times the size of the normal adrenal gland]) within 3 years prior to Screening.
5. 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).
   - Systolic hypertension (average SBP ≥130 to ≤170 mm Hg) based on 24-hour ABPM (Parati et al. 2014).
6. 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.
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 (average SBP >170 mm Hg or average DBP >110 mm Hg at Screening), based on 24-hour ABPM.
2. Has poorly controlled DM (HbA1c >12% at Screening).
3. Has DM Type 1.
4. Has abnormal liver test results (total bilirubin >1.5×ULN or elevated alanine aminotransferase or aspartate aminotransferase >3×ULN at Baseline).
5. Has severe renal insufficiency (glomerular filtration rate ≤29 mL/min/1.73 m^2 at Baseline).
6. Has uncontrolled, clinically significant hypothyroidism or hyperthyroidism.
7. 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).

8. Has persistent atrial fibrillation.
9. Has used or plans to use any treatments for Cushing syndrome within 12 weeks prior to Screening and throughout the study, including mifepristone, metyrapone, osilodrostat, ketoconazole, fluconazole, or any investigational drug for treatment of Cushing syndrome.
10. Patients who require inhaled glucocorticoids and have no alternative option if their condition deteriorates during the study.
11. Has adrenocortical carcinoma.
12. 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.
13. Has a history of cyclic Cushing syndrome with fluctuating clinical manifestations.
14. Has autonomous cosecretion of aldosterone.
15. Has plans for adrenalectomy or nodulectomy during the study, including follow-up.
16. Has taken any non-Cushing syndrome investigational drug within 4 weeks prior to Baseline, or within less than 5 times the drug's half-life, whichever is longer.
17. 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.
18. Ongoing use of any strong CYP3A4 inducer or any other prohibited medications (see Section 5.6).
19. Is pregnant or lactating.
20. Is a female patient of childbearing potential who cannot use a highly effective method of contraception (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); see Section 4.6.2.
21. Has an acute or unstable medical problem that could be aggravated by treatment with the investigational study drug.
22. Has a history of severe reaction to the study drug, to a similar class of drug, or to the study drug's excipient.
23. In the Investigator's opinion, should not participate in the study or may not be capable of following the study schedule.
24. Has known HIV, hepatitis B, or hepatitis C infection and is taking medication for treatment of HIV, hepatitis B, or hepatitis C infection.
25. Has used mitotane prior to Baseline.

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 of relacorilant or matched placebo once daily. From Visit Week 2 to visit Week 10, the dose will be increased every 4 weeks—to 200 mg at Week 2, to 300 mg at Week 6, and to 400 mg at Week 10—based on tolerability and improvement in hyperglycemia and/or hypertension. If a dose is not tolerated, dose interruption, dose reduction, and dose re-escalation are allowed.

Patients will maintain a once-daily dose of 400 mg, or their highest tolerated dose.

Pharmacokinetics

Blood concentrations of relacorilant will be measured and PK examined in all patients at Visit Week 18.

Statistical Methods

Analysis Populations

Safety: All patients randomly assigned to study treatment and who take ≥1 dose of study treatment. Patients will be analyzed according to the treatment they actually received.

Intent-to-treat (ITT): All patients who were randomized to receive relacorilant or placebo, even if they do not receive any study treatment. This population will be used for the analysis of the primary and secondary efficacy endpoints. Analyses of blood-pressure control measures will be performed on all patients in the ITT population with hypertension, regardless of whether they have DM/IGT at Baseline. Analyses of measures of glycemic control will be performed on all patients in the ITT population with DM/IGT, regardless of whether they have hypertension at Baseline.

Modified ITT (mITT): All patients in the ITT population with ≥1 post-randomization efficacy assessment for the primary and secondary efficacy endpoints of ABPM and/or $AUC_{glucose}$. This population will be used for sensitivity analyses performed on the primary and secondary efficacy endpoints. The mITT population can vary for different efficacy endpoints.

PK: The subset of the Safety population with adequate PK data.

PD: The subset of the Safety population with adequate PD data.

Statistical Analyses

For the testing of the primary and certain secondary efficacy endpoints, adjustment for multiplicity will be implemented to maintain a 2-sided 0.05 significance level for the Family-Wise type I error rate.

In order to provide strong control of the Type I error, certain secondary analyses will be tested using a gated testing approach at a 2-sided alpha level of 0.05. If the null hypothesis is rejected for the primary endpoint, certain secondary endpoints will be sequentially tested following the gatekeeping hierarchy as follows:

1. Mean change in average daytime SBP based on ABPM (06:00-21:59),
2. mean change in average nighttime SBP based on ABPM (22:00-05:59),
3. mean change in weight,
4. mean change in $AUC_{glucose}$,
5. mean change in 2-hour oGTT 2-hour timepoint, and
6. mean change in 2-hour oGTT predrink timepoint.

No adjustments for multiplicity will be made for other secondary or exploratory endpoints.

All statistical hypotheses for any other secondary endpoints and exploratory endpoints will be tested at a 2-sided 0.05 significance level unless otherwise specified.

Analysis of Primary Efficacy Endpoint

For the hypertension subgroup of the ITT Population, the estimand of interest is the between-treatment difference in change in average SBP based on 24-hour ABPM from Randomization to Week 22 (estimated using a MMRM model) regardless of treatment discontinuation and as if rescue medication was not available.

For patients who use rescue medication or discontinue treatment early, a placebo wash-out multiple imputation will be used as the primary analysis. For those patients who use rescue medication for hypertension after randomization and before Visit Week 22, the values collected after first use of rescue medication are irrelevant to the clinical question of interest and will not be used in the

analysis. For patients who discontinue treatment early, all collected values (including retrieved drop-outs) will be used in the analysis.

The 'placebo wash-out' analysis means the missing 24-hour average SBP at Visit Week 22 data will be imputed by considering a wash-out of the effect of treatment using completers in the placebo arm. Additional details are presented in the SAP. The primary efficacy analysis for the primary endpoint of change in 24-hour average SBP from Randomization to Week 22 will be performed using a linear mixed-model-for-repeated-measures (MMRM) using data with the imputation method described above. Restricted maximum likelihood (REML) estimation will be used. The MMRM model will include Baseline average SBP based on 24-hour ABPM as a covariate; treatment, visit, and treatment by visit interaction, and stratification factor as fixed effects; patients within treatment groups as random effects. In the hypertension subgroup, the stratification factor at randomization identifies patients with or without DM/IGT. 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.

The primary analysis will determine whether there is a difference between treatment groups in terms of change in 24-hour average SBP from Randomization to Week 22. This will be accomplished by using appropriate linear contrasts of the parameters in the MMRM model described above.

Multiple imputation will be implemented to allow additional source of variability in the imputed values. For each imputed dataset, the same MMRM model specified above will be used to estimate treatment effect on change in average SBP based on 24-hour ABPM from Randomization to Week 22. The combination of individual estimates for treatment effect and the inference based on the combined estimate will be handled by SAS procedure MIANALYZE. Additional sensitivity analyses of the primary endpoint, including subgroups of interest, will be specified in the SAP.

Analysis of Secondary Efficacy Endpoints

For continuous endpoints in 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 Baseline value (for the respective endpoint) as a covariate; treatment, visit, treatment by visit interaction, and stratification factor (at randomization) 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.

The analysis for each of the endpoints will determine whether there is a difference between treatment groups in terms of change from Randomization to Week 22. 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 endpoints described as proportions in the study, the point estimate and the 2-sided 95% CI will be calculated. A logistic model including effects for treatment, continuous baseline value, and stratification factor at randomization will be used to assess differences in proportions between treatment arms (Steingrimsson et al. 2017).

Safety Analyses

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

TEAEs will be summarized by treatment group. Serious AEs and TEAEs that lead to study-drug withdrawal or withdrawal from the study will be summarized by treatment group and listed by patient.

TEAEs will be summarized by 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.

Clinical laboratory test results (chemistry and hematology), vital sign measurements, and ECG interval results will be summarized as changes from baseline by parameter and visit using descriptive statistics. Shift tables will describe changes from Baseline in clinical laboratory values.

Sample-Size Calculation

Approximately 130 patients are planned to be randomized into the study.

Attainment of the randomization targets within the DM/IGT and hypertension subgroups in this study assumes that 40% of randomized patients will have DM/IGT only, 40% will have hypertension only, and 20% will have both DM/IGT and hypertension. This projected sample size will result in randomization of approximately 78 patients with DM/IGT (with or without hypertension) and 78 patients with hypertension (with or without DM/IGT).

Seventy-eight patients with DM/IGT (39 patients per treatment group) will ensure at least 90% power to detect a difference of 3.1 h*mmol/L in mean changes in $AUC_{glucose}$ (based on the 2-hour oGTT measurement) between placebo and treatment arm. This calculation assumes a common standard deviation of 3.7 h*mmol/L, and a 0.025 two-sided significance level two sample t-test. Twenty percent dropout rate from Baseline to Week 22 is assumed in this calculation.

Seventy-eight patients with hypertension (39 per treatment group) will ensure at least 90% power to detect a difference between placebo and treatment arms in average SBP of 7 mm Hg (based on ABPM). These calculations assume a common standard deviation of 8 mm Hg and a 0.025 two-sided significance level two-sample t-test. Twenty-eight percent dropout rate from Baseline to Week 22 is assumed in this calculation.

In summary, the expected randomization of 130 patients in the study will result in 78 patients within each of the DM/IGT and hypertension subgroups. This sample size will provide sufficient power to detect the target differences in the primary endpoint for each of the subgroups.

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LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
ABPM	ambulatory blood pressure monitoring
ACTH	adrenocorticotropic hormone
AE	adverse event
ALT	alanine aminotransferase (SGPT)
AST	aspartate aminotransferase (SGOT)
AUC	area under the concentration-time curve
$AUC_{0–24h}$	AUC values from time 0 to 24 hours postdose
$AUC_{glucose}$	area under the concentration-time curve for glucose
AUC_{inf}	AUC values from time 0 extrapolated to infinity
AUC_{last}	AUC values from time 0 to time of last measurable concentration
BDI-II	Beck Depression Inventory®-II
BP	blood pressure
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum concentration
C_{min}	minimum concentration within a dose interval
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DBP	diastolic blood pressure
DHEA-S	dehydroepiandrosterone sulfate
DM	diabetes mellitus
DRB	Data Review Board
DST	dexamethasone suppression test
DXA	dual-energy X-ray absorptiometry
ECG	electrocardiogram
EC	Ethics Committee
EMA	European Medicines Agency
eCRF	electronic case report form
ET	early termination
FDA	(United States) Food and Drug Administration
FKBP5	FK506-binding protein 5

Abbreviation	Definition
FU	follow-up
GAPDH	glyceraldehyde 3-phosphate dehydrogenase
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GR	glucocorticoid receptor
HbA_{1c}	hemoglobin A_{1c}
Hgb	hemoglobin
HOMA IR	homeostatic-model assessment of insulin resistance
HPA	hypothalamic-pituitary-adrenal
ICF	informed consent form
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IGT	impaired glucose tolerance
IHC	immunohistochemistry
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	intent-to-treat
K_i	inhibition constant
m-RNA	messenger RNA
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MR	mineralocorticoid receptor
oGTT	oral glucose tolerance test
PD	pharmacodynamic
PK	pharmacokinetic
PR	progesterone receptor
PTT	partial thromboplastin time
QoL	quality-of-life
QTc	corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's equation: $QTcF=QT/(RR^{1/3})$
REB	Research Ethics Board

Abbreviation	Definition
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SEM	standard error of the mean
SOA	schedule of activities
SOC	system organ class
$t_{1/2}$	apparent terminal elimination half-life
TAT	tyrosine aminotransferase; thrombin antithrombin
TEAE	treatment-emergent adverse event
UFC	urinary free cortisol
ULN	upper limit of normal
US	United States
WBC	white blood cell (count)

1 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 Therapeutic Area

Hypercortisolism, often referred to as Cushing syndrome, is caused by excessive activity of the hormone cortisol. Endogenous Cushing syndrome is a rare endocrine disease associated with prolonged exposure to abnormally high levels of cortisol. Clinical manifestations vary, but most patients experience one or more of the following: hyperglycemia, hypertension, central obesity, facial plethora, abnormal fat distribution (supraclavicular fat pads and "buffalo hump"), proximal muscle weakness, skin thinning, and easy bruising. Irritability, anxiety, depression, sleep, and cognitive disturbances are also common.

Establishing the diagnosis of Cushing syndrome is often difficult because few of the symptoms or signs are pathognomonic of the syndrome in isolation. There is a large variation in disease severity, depending on duration and intensity of excess cortisol production. Furthermore, some disease manifestations (e.g., as hypertension, obesity, and glucose intolerance) are common in individuals who do not have cortisol excess. The diagnosis of Cushing syndrome involves three steps: 1) suspecting it based on the patient's signs and symptoms, 2) documenting the presence of hypercortisolism, and 3) determining the cause of hypercortisolism.

Determination of the cause of hypercortisolism requires an understanding of the pathophysiology of the different types of Cushing syndrome. Cushing syndrome may be either adrenocorticotropic hormone (ACTH) dependent or ACTH independent. The most common cause of overt Cushing syndrome is ACTH-secreting pituitary tumors, followed by cortisol-secreting adrenal tumors or hyperplasia. Ectopic Cushing syndrome, which can produce severe manifestations of excessive cortisol activity, is a rare form of Cushing syndrome secondary to nonpituitary, ACTH-secreting tumors (benign or malignant). For patients with overt endogenous Cushing syndrome, there is consensus about the need for treatment, with surgical resection of the ACTH-or cortisol-secreting tumor as the first-line treatment. In cases in which surgery has failed, or is not an option, medical therapy targeting cortisol synthesis or cortisol activity is used.

Management of patients with milder forms of Cushing syndrome, in particular those with cortisol-secreting adrenal adenomas or hyperplasia, is more challenging. Although these patients lack many of the more specific signs of 'overt' Cushing syndrome (Cushingoid appearance, proximal muscle weakness, easy bruising, and striae), they frequently have one or more of the less-specific comorbidities associated with elevated cortisol, including hypertension, diabetes mellitus (DM)/impaired glucose tolerance (IGT), central obesity, dyslipidemia and osteoporosis (Fassnacht et al. 2016).

Several surgical series in patients with cortisol-secreting adrenal masses have failed to consistently demonstrate a causal relationship between hypercortisolism and comorbidities common in the general population (e.g., hyperglycemia, hypertension, dyslipidemia, and obesity). In some reports, a significant proportion of patients undergoing surgery experienced improvement of cortisol-excess-related comorbidities (e.g., hypertension, DM/IGT, obesity) (Toniato et al. 2009, Bancos et al. 2016). For example, Toniato, et al reported that post adrenalectomy and normalization of cortisol and ACTH levels, approximately half of

patients experienced normalization of obesity, and approximately 40% and 80% of patients had normalization/improvement of hyperglycemia and hypertension, respectively (Toniato et al. 2009). Similar to Toniato's study, several other surgical series showed that clinical improvement is often observed with adrenalectomy, but not in every case (Fassnacht et al. 2016).

The European Endocrine Society recommends considering the risk of malignancy in helping determine whether surgery is the proper course for the management of adrenal incidentalomas (Fassnacht et al. 2016). For patients with bilateral adrenal tumors, unilateral adrenalectomy can significantly improve the disease (Bancos et al. 2016). However, due to continuous growth of the contralateral gland, relapse is common. Resection of the second adrenal gland, or bilateral adrenalectomy as a first-line therapy, is associated with primary adrenal insufficiency, which requires lifelong treatment with glucocorticoid and mineralocorticoid analogues and significant morbidity.

If hypercortisolism in the presence of an adrenal adenoma or hyperplasia is suspected, abnormal cortisol secretion is demonstrated using the 1mg overnight dexamethasone suppression test (DST). Historically, the cortisol cut-off following the DST to make a diagnosis has been a source of debate in the endocrine community. But in 2015, the European endocrine guidelines for adrenal incidentalomas agreed to interpret the results of this test using a continuous variable rather than a categorical one (i.e., using a numerical value instead of Yes/No) (Fassnacht et al. 2016). By these guidelines, a value ≤1.8 µg/dL (50 nmol/L) is considered 'normal'. This cut-off value is supported by studies demonstrating that patients with post-dexamethasone cortisol values >1.8 µg/dL) have increased morbidity or mortality. For patients with post-DST serum cortisol of 1.9–5.0 µg/dL (51–138 nmol/L), and without overt Cushing syndrome, the committee proposed the term 'possible autonomous cortisol secretion'. For patients with higher values, the term 'autonomous cortisol secretion' was proposed (Fassnacht et al. 2016).

Although surgery is usually recommended in patients who have a DST >5 µg/dL and the presence of 2 or more comorbidities (at least one of which is poorly controlled by medical treatment), there remains a lack of consensus on the optimal treatment approach (i.e., surgery vs. symptomatic treatment of comorbidities) for patients with adrenal adenoma and post-DST serum cortisol between 1.9–5.0 µg/dL.

Although patients with cortisol-secreting adrenal lesions do not often progress into overt Cushing syndrome, they may develop comorbidities, including hypertension, DM/IGT, and dyslipidemia, and currently it is not possible to predict which patients might benefit from adrenalectomy (Zografos et al. 2014, Elhassan et al. 2019, Fassnacht et al. 2016).

Recent retrospective studies have demonstrated an association between hypercortisolism and cardiovascular and bone abnormalities (Debono et al. 2014, Debono et al. 2013), and it has been reported that patients with milder forms of Cushing syndrome do not receive specific treatment for their hypercortisolism and instead receive symptomatic treatment of their metabolic and cardiovascular symptoms (Zografos et al. 2014). Although there is accumulating evidence to support the role of cortisol in the disease profile of these patients, direct management of the underlying hypercortisolism is not standard clinical practice (Fassnacht et al. 2016, Chiodini et al. 2019, Morelli et al. 2016, Zografos et al. 2014).

Other treatment options for hypercortisolism have limitations in the setting of adrenal adenoma or hyperplasia. Agents targeting ACTH secretion (pasireotide) are not beneficial for ACTH-independent hypercortisolism. For cortisol-synthesis inhibitors (e.g., ketoconazole, metyrapone, and mitotane), the normalization of urinary free cortisol (UFC) is used to monitor titration to avoid overtreatment and ensuing adrenal insufficiency. Patients with cortisol-secreting adrenal adenomas, however, do not usually present with elevated UFC levels. Glucocorticoid receptor (GR) antagonists, which are titrated via clinical efficacy and tolerability and not UFC measurements, could play a useful role in the management of hypercortisolism due to adrenal adenoma/hyperplasia. The concept of using GR antagonists for the management of hypercortisolism due to adrenal adenoma is similar to the use of aldosterone-receptor antagonists for the treatment of primary aldosteronism.

Mifepristone, the first GR antagonist to become available for the treatment of patients with Cushing syndrome in the US, was approved following an open-label study demonstrating clinical improvement in glucose control. In the pivotal trial with mifepristone, all patients had overt Cushing syndrome; there were no patients with benign adrenal tumors. Case reports and small case series in patients with autonomous cortisol secretion treated with mifepristone demonstrated improvement in hyperglycemia and weight loss similar to the surgical series (Belokovskaya et al. 2019, Debono et al. 2013). However, a smaller effect on hypertension was seen. The lack of as strong an effect on hypertension is likely due to the significant increase in ACTH levels following treatment with mifepristone, which stimulates secretion of additional cortisol from the adrenal adenoma and normal cortisol-secreting cells of the adrenal cortex, which, in turn, stimulates the mineralocorticoid receptor (MR).

Relacorilant (CORT125134) is a next-generation GR antagonist being developed for the treatment of Cushing syndrome and other conditions that was designed to overcome adverse effects of mifepristone.

1.2 Relacorilant

Relacorilant is a selective, high-affinity antagonist of the GR (inhibition constant <1 nM in a human GR binding assay and <10 nM in a human functional assay) and it has considerably greater selectivity for GR over the progesterone receptor (PR), producing only 7% displacement of labelled progesterone at a concentration of 1 µM (relacorilant K_i >10 µM, mifepristone K_i=1.2 nM) in a PR ligand binding assay (Cerep Report 100011862). Given this 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. The effect of relacorilant on the pituitary also appears to be smaller compared with mifepristone—ACTH levels appear to be less affected in both patients with ACTH-dependent and adrenal Cushing syndrome (CSR CORT125134-451), which offers a potential advantage of relacorilant over mifepristone in the treatment of patients with hypercortisolism due to adrenal adenoma or hyperplasia.

1.3 Clinical Summary

A brief summary of relacorilant clinical studies is presented (Sections 1.3.1 and 1.3.2). Further details on pharmacology, absorption, distribution, metabolism, and elimination (ADME), and toxicology of relacorilant are presented in the Investigator's Brochure.

1.3.1 Phase 1 Studies

In a 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 of the 'clinical-pharmacology' formulation (an earlier formulation with a higher bioavailability than the current 'clinical-trial formulation'). In this study, a single dose of 500 mg or multiple doses of 250 mg of relacorilant along with a high dose of prednisone in healthy subjects showed prevention of the changes induced by prednisone alone in several glucocorticoid-induced biomarkers, including osteocalcin, lymphocytes, eosinophils, and FKBP5 mRNA levels. Single doses of relacorilant up to 500 mg daily were well tolerated. 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 (SOC) musculoskeletal and connective tissue disorders.

Two additional studies in healthy volunteers (Study CORT125134-453, Study CORT125134-126), with multiple doses of relacorilant have been completed. In Study CORT125134-453, in which multiple doses of 150 mg, 250 mg, and 350 mg relacorilant daily, the most commonly reported TEAEs were musculoskeletal, connective tissue, GI, and nervous system related. The most commonly reported TEAE were headache, for which a dose-related trend was reported (12.5%, 25.0%, and 37.5% of subjects following dosing with 150 mg, 250 mg, and 350 mg relacorilant daily, respectively), and back pain, which was reported at the 350 mg dose level only, in 50% of subjects. Similar safety results were observed in Study CORT125134-126.

In the drug-drug interaction Study CORT125134-126, relacorilant exhibited no relevant effect on exposure to probe substrates for CYP2D6, CYP2C8, CYP2C9, or CYP2C19. However, relacorilant was shown to be a strong CYP3A inhibitor of the probe substrate midazolam, resulting in AUC extrapolated to infinity (AUC_{inf}) and C_{max} of 8.8-fold and 3.3-fold higher, respectively, relative to midazolam alone.

Study CORT125134-129 was conducted with relacorilant 400 mg (4 × 100 mg [redacted] capsule; clinical-trial formulation that is also considered the "to-be-marketed" formulation). Following administration of relacorilant under fed conditions with a low-fat meal, relacorilant C_{max} and AUC_{inf} increased approximately 69% and 2.0-fold, respectively, relative to relacorilant administered under fasting conditions. Following administration of relacorilant under fed conditions with a high-fat meal, relacorilant C_{max} and AUC_{inf} increased approximately 92% and 2.4-fold, respectively, relative to relacorilant administered under fasting conditions.

1.3.2 Phase 2 Study

A total of 35 patients were included in the Safety Population of this Phase 2, open-label, multicenter, dose-escalation study in patients with endogenous Cushing syndrome (Study CORT125134-451; NCT02804750). 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). Relacorilant exposure remained well below the 40 µg•h/mL cap (exposure limit guided by results of the toxicology studies) at all doses.

Overall, 94.3% of patients experienced TEAEs. In Group 1, 15/17 (88.2%) patients experienced a total of 101 TEAEs. The most common (≥20%) TEAEs in Group 1 were back pain, diarrhea, headache, and pain in extremity (23.5% each). In Group 2, all 18 patients (100%) experienced a total of 228 TEAEs. The most common (≥20%) TEAEs in Group 2 were back pain (38.9%), headache and nausea (27.8% each), and abdominal pain, arthralgia, dizziness, dyspepsia, myalgia, and pain in extremity (22.2% each).

There were no TEAEs resulting in death during the study. Four (11.4%) patients experienced treatment-emergent SAEs (TESAEs); no TESAEs were reported in Group 1 and 5 TESAEs (in 4 patients) were reported in Group 2. All TESAEs were Grade 3 in severity. Three (8.6%) patients had TESAEs (polyneuropathy, myopathy, and acute myocardial infarction) that were considered possibly related to study drug by the Investigator and led to study-drug discontinuation. These TESAEs were considered not related to the study drug by the Sponsor.

Because relacorilant affects cortisol action and not cortisol secretion, measuring cortisol levels is not a suitable method to monitor the treatment effect. Therefore, the efficacy of relacorilant in this study was measured based on improvement of cortisol-excess-related comorbidities (e.g., hyperglycemia and hypertension).

For patients with DM at Baseline, a decrease in HbA1c by ≥0.5% from Baseline to the last visit, normalization of the 2-hour oGTT glucose (<140 mg/dL)/decrease by ≥50 mg/dL from Baseline to last visit, or decrease in total daily insulin dose by ≥25% (with HbA1c unchanged or decreased compared with Baseline) was considered a clinically meaningful response. For patients with IGT at Baseline, normalization of the 2-hour oGTT glucose was considered a response. In the mPP Population (IGT/diabetes subgroup), 2 of 13 (15.38%) patients (95% CI lower bound 1.92%) in Group 1 and 6 of 12 (50%) patients (95% CI lower bound 21.09%) in Group 2 met at least one of the above response criteria.

For patients with uncontrolled hypertension at Baseline, a decrease of ≥5 mm Hg decrease in mean systolic BP (SBP) and/or diastolic BP (DBP) from Baseline to last visit, without worsening of either, based on 24-hour ambulatory BP monitoring (ABPM), was considered a response. Among patients with hypertension, 41.7% of patients in Group 1, and 63.6% of patients in Group 2 responded.

In summary, this Phase 2 study of relacorilant (Study CORT125134-451), demonstrated clinical improvement in glucose control and in hypertension in patients with Cushing syndrome. There was also improvement in several comorbidities associated with cortisol excess, including improvement in quality of life and other comorbidities including CNS manifestations (e.g., depression and cognitive impairment), bone metabolism, coagulation parameters, and liver function tests.

1.4 Rationale for Study Design and Dose Regimen

1.4.1 Design Considerations

This will be a Phase 3, randomized, double-blind, placebo-controlled study conducted in the US, Europe, and Israel at approximately 60 sites. Approximately 130 patients will be randomized 1:1 to relacorilant or placebo.

The study proposed here specifically targets patients with hypercortisolism due to cortisol-secreting adrenal adenomas or hyperplasia. These patients may or may not present the classic clinical manifestations of overt Cushing syndrome (i.e., facial appearance, buffalo hump, striae, etc.). Although adrenal tumors are frequently detected incidentally during abdominal imaging studies (incidentalomas), especially in older patients, up to 29% of these tumors secrete cortisol (Fassnacht et al. 2016).

Because of the mechanism of action of relacorilant, a GR antagonist that does not affect cortisol levels, efficacy will be assessed by monitoring clinical manifestations frequently associated with cortisol excess—hyperglycemia (DM/IGT) and hypertension. Two robust and validated clinical measures of blood glucose control and blood pressure (BP) control, will be used. For patients with hyperglycemia, glucose metabolism and insulin resistance will be evaluated with the oGTT. The secondary endpoint of the mean change in the $AUC_{glucose}$ was chosen because it reflects glucose control in patients with diabetes as well as those with IGT, for whom neither HbA1c nor fasting glucose are reliable measures of glucose control. The primary endpoint of mean change in SBP was chosen because adrenal adenomas are usually diagnosed in older patients for whom systolic hypertension is most frequently observed (diastolic hypertension is more frequently observed in younger patients). This endpoint uses 24-hour ambulatory blood pressure monitoring (ABPM), which is considered the gold-standard measurement.

To examine the many manifestations of cortisol excess in the study patients, several other efficacy assessments will be used to assess clinical benefit, including assessment of Quality-of-Life, bone microarchitecture, weight, whole-body fat composition, coagulation markers, and lipid profile.

1.4.2 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 and safety, efficacy, and PK results in a Phase 2 study in patients with Cushing syndrome (CORT125134-451) (see Section 1.3.2). Across all studies, exposure to relacorilant (as $AUC_{0\text{-}24h}$) at steady-state was well below the toxicology threshold and was consistent between healthy subjects and patients with Cushing syndrome. The PK of relacorilant support once-daily dosing.

In the Phase 2, open-label, multicenter Study CORT125134-451, 35 patients with endogenous Cushing syndrome received daily relacorilant in escalating doses ranging from 100–200 mg (Group 1, 12 weeks) or from 250–400 mg (Group 2, 16 weeks).

Efficacy results indicate that treatment with relacorilant in patients with endogenous Cushing syndrome leads to 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. In Group 2, most responders start achieving clinical benefit at the starting dose of 250 mg daily, although some patients required doses up to 400 mg daily for optimal benefit.

There was, however, a difference in the TEAEs between the two groups. In Group 1, treatment was generally well tolerated. In Group 2, patients experienced TEAEs (especially musculoskeletal symptoms) at a higher frequency and with greater intensity compared with patients in Group 1. Although the maximum dose of relacorilant in Group 1 (200 mg) was very well tolerated, every patient in Group 2 experienced TEAEs at the starting dose of relacorilant of 250 mg daily, despite the fact that the levels of relacorilant at the highest dose of Group 1 (i.e., 200 mg) were similar to the levels achieved with the starting dose of relacorilant in Group 2 (250 mg). The frequency of TEAEs in Group 2 decreased with continuous therapy with relacorilant at the same or higher dose indicating that most of those TEAEs were consistent with cortisol-withdrawal symptoms, commonly seen in patients starting on an effective dose of a Cushing syndrome medication without preceding titration. Therefore, the approach in this study is to titrate the relacorilant dose from a starting dose of 100 mg, which was well tolerated in the Phase 2 study, to higher potentially more efficacious doses.

1.5 Risk/Benefit Assessment

The United States (US) Food and Drug Administration (FDA), as well as the European Medicines Agency (EMA), acknowledge the impact of coronavirus disease 2019 (COVID-19) on the health system and broader society, and recognize the impact it could have on trials and trial participants (FDA 2021, EMA 2022). 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 CORT125134-456, 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 trial 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 modifying 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 prioritize 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 for COVID-19.

COVID-19 measures cited in this protocol amendment are temporary and will be repealed back to previous state when the situation (governmental rules, benefit/risk assessment for the trial) allows.

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). Relacorilant antagonizes the GR similar to mifepristone, but has no effect on the PR. Relacorilant is therefore expected to effectively treat hypercortisolism, without the drawbacks of PR antagonism that may result in untoward reproductive effects, which may lead to 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 well tolerated, with the most common side effects observed at higher doses. Compared with the predecessor drug mifepristone, relacorilant offers two key safety advantages—lack of affinity for the PR, and lack of significant cortisol rise (which is mostly responsible for the hypokalemia and worsening hypertension observed with 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, nausea, vomiting, and muscle aches. Since relacorilant does not affect the MR, it is unlikely that hypotension would occur in the absence of antihypertensive medication. Because plasma glucocorticoid levels are not decreased with relacorilant administration, a single laboratory test 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 may be given to overcome the GR antagonism (see Section 5.4.1).

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

Patients receiving placebo cannot expect a meaningful improvement of the manifestations of their hypercortisolism. However, these tumors progress very slowly, and rarely progress into overt Cushing syndrome (Fassnacht et al. 2016). Thus, no significant worsening of the clinical manifestations of hypercortisolism is expected in the placebo group during the study.

Relacorilant is metabolized by multiple CYP enzymes, including CYP3A and CYP2C8, and by carbonyl reductases. Relacorilant is a strong inhibitor of CYP3A. If a concomitant medication is required to treat an AE, the Investigator must consider the risk of drug-drug interaction.

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. Because dual-energy X-ray absorptiometry (DXA) scans use X-ray energy, there is risk due to exposure radiation. The total volume of blood collected will not exceed 505 mL, unless the Investigator or designee considers additional unplanned collection(s) are required for safety laboratory tests.

Because the study is placebo controlled, measures are in place (Section 5.5) to allow patients to receive treatment for comorbid conditions as necessary.

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

2 STUDY OBJECTIVES

2.1 Primary Objectives

- To assess the efficacy of relacorilant for the treatment of hypercortisolism in patients with cortisol-secreting adrenal adenomas or hyperplasia, based on blood pressure (BP) control at Week 22 compared with placebo
- To assess the safety of relacorilant for the treatment of hypercortisolism

2.2 Secondary Objective

- To assess changes in cortisol excess-related comorbidities (e.g., body weight and glycemic control) in patients with hypercortisolism due to cortisol-secreting adrenal adenomas/hyperplasia

2.3 Exploratory Objectives

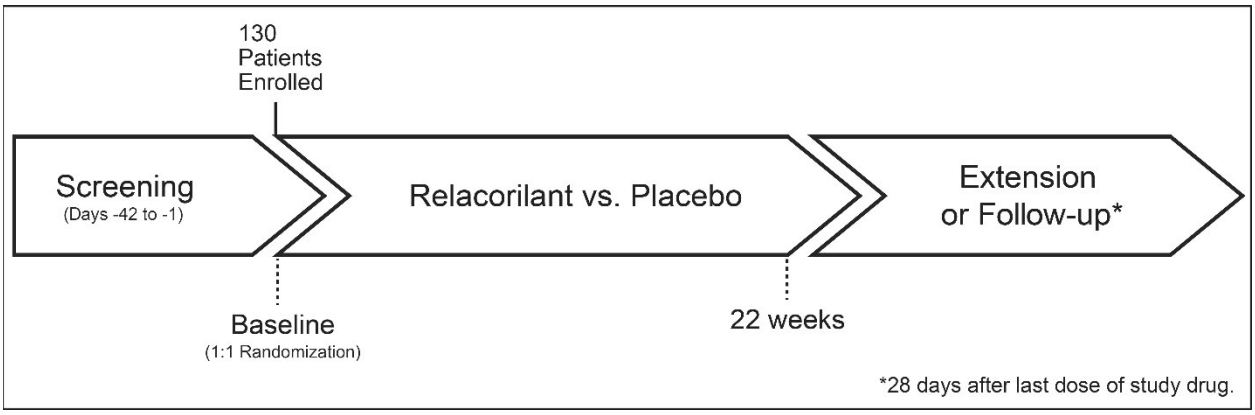
- To explore changes in cortisol excess-related comorbidities including assessments of glucose, insulin resistance indices, coagulation markers, GR activity biomarkers, HPA axis, and bone turnover markers, depression and quality of life questionaries in patients with cortisol-secreting adrenal adenomas or hyperplasia
- To assess the pharmacokinetics of relacorilant in patients with hypercortisolism due to cortisol-secreting adrenal adenomas/hyperplasia

3 STUDY DESIGN

3.1 Overall Design

This is a Phase 3, double-blind, placebo-controlled study to assess the efficacy, and safety of relacorilant to treat hypercortisolism in patients with cortisol-secreting adrenal adenoma or hyperplasia associated with DM/IGT and/or uncontrolled systolic hypertension. Two subgroups—DM/IGT and hypertension—will be analyzed.

Figure 1 CORT125134-456 Study Design



3.2 Study Endpoints

3.2.1 Primary Endpoints

In patients with systolic hypertension, the mean change in 24-hour average SBP based on 24-hour ABPM, from Baseline to Week 22 as compared between relacorilant and placebo arms.

In all patients, assessment of safety based on TEAEs.

3.2.2 Secondary Endpoints (from Baseline to Week 22/ET, compared between relacorilant and placebo)

Endpoints for Hypertension

1. In patients with systolic hypertension at Baseline, mean change in average DBP and HR (based on 24-hour ABPM).
2. In patients with systolic hypertension at Baseline, mean change in daytime average SBP, DBP, and HR (based on 24-hour ABPM).
3. In patients with systolic hypertension at Baseline, mean change in nighttime average SBP, DBP, and HR (based on 24-hour ABPM).
4. In patients with systolic hypertension at Baseline, proportion of patients with any dose increase in antihypertensive medications due to worsening hypertension.
5. In patients with systolic hypertension at Baseline, proportion of patients with a reduction in 24-hour average SBP by 5 mm Hg (based on 24-hour ABPM).
6. In patients with systolic hypertension at Baseline, proportion of patients with any dose decrease in antihypertensive medication due to improved blood pressure.

7. In patients with systolic hypertension at Baseline, proportion of patients with normalization of the average SBP (<130 mm Hg, based on 24-hour ABPM).

Endpoints for Hyperglycemia

1. In patients with DM/IGT at Baseline, the mean change in $AUC_{glucose}$, from Baseline to Week 22 as compared between relacorilant and placebo arms.
2. In patients with DM (HbA1c at Baseline ≥6.5%), the mean change in HbA1c.
3. In patients with DM/IGT (HbA1c at Baseline ≥5.7%), the mean change in HbA1c.
4. Proportion of patients with HbA1c ≥6.5% at Baseline who achieved HbA1c <6.5%.
5. In patients with DM at Baseline, proportion of patients who achieved 2-hour oGTT glucose <140 mg/dL.
6. In patients with IGT at Baseline, proportion of patients who achieved 2-hour oGTT glucose <140 mg/dL.
7. In patients with DM/IGT at Baseline, proportion of patients with any dose decrease of diabetes medication due to improved glucose control.
8. In patients with DM/IGT at Baseline, proportion of patients with any dose increase of diabetes medications due to worsening hyperglycemia.
9. In patients with DM/IGT in the ITT population, the proportion of patients who achieved decrease of $AUC_{glucose}$ of ≥25%, ≥10%, ≥5% and any decrease from Baseline to Week 22.
10. In patients with DM/IGT in the ITT population, the mean change in 2-hour oGTT 2-hour timepoint from Baseline to Week 22.
11. In patients with DM/IGT in the ITT population, the mean change in 2-hour oGTT predrink timepoint from Baseline to Week 22.

Other Secondary Endpoint

1. In all patients, the mean change in body weight and waist circumference.

3.2.3 Exploratory Efficacy Endpoints

The mean change from Baseline to Week 22/ET in serum osteocalcin; in trabecular bone score, bone mineral density, and body composition from DXA scans; the Beck Depression Inventory®-II (BDI-II) score; sit-to-stand test score; trail making test scores; coagulation markers (Factor VIII, von Willebrand factor, protein S, protein C, TAT, platelets, and PTT); biomarkers related to GR activity (such as FKBP5); DHEA-S concentrations; ACTH concentrations; lipids (total cholesterol, LDL cholesterol, triglycerides, and very-low-density lipoprotein cholesterol); HPA-axis; difference between morning and late-night salivary cortisol; $AUC_{glucose}$; fasting glucose in patients with DM; insulin resistance indices and hyperglucagonemia ($AUC_{insulin}$, Matsuda Index, homeostatic model assessment of insulin resistance [HOMA IR], and at selected visits $AUC_{glucagon}$), and Cushing Quality-of-Life (Cushing QoL) score.

Intensive pharmacokinetic blood sampling will be conducted in all patients at the Week 18 visit. The plasma concentrations of relacorilant and/or its metabolites will be examined.

3.3 Number of Patients and Study Duration

3.3.1 Number of Patients

Approximately 130 patients will be randomized.

3.3.2 Study Duration

The maximum expected duration of a patient's participation is 32 weeks, including up to 6 weeks for Screening, 22 weeks of double-blind treatment, and a follow-up visit 28 days after the last dose of study drug.

3.3.3 Discontinuation of Study Sites

Participation of a study site may be discontinued if the Sponsor, its designee, the Investigator, or the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) determines it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and guidelines.

3.4 Definitions

3.4.1 Enrollment

Patients are considered enrolled in the study when they have signed the ICF, been screened, and their eligibility has been verified.

3.4.2 End of Treatment

The end of treatment is defined as the date on which the patient received his or her last treatment, which may be the end of the Treatment Period if the patient completed all treatments or may be earlier if the patient discontinued study treatment before the designated stopping point at Week 22.

3.4.3 Patient Study Completion

Patients who complete 22 weeks of the double-blind, placebo-controlled phase and return for the follow-up visit 28 days after the last dose of study drug will be considered to have completed the study. The follow-up visit will serve as the last study visit.

Patients who complete 22 weeks of the double-blind, placebo-controlled phase, and enter an extension study without interruption will also be considered to have completed the study; in that case the follow-up visit will not be required, and Week 22 will serve as the last study visit.

3.4.4 End of Study

The end of study is defined as the date of last contact (visit, telephone, e-mail) with the last patient in the study. The Sponsor 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 Treatment Continuation

Patients who complete the study will be permitted to continue relacorilant treatment in an extension study provided that they have at least 80% adherence with scheduled dosing (by capsule counts). 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 the Week 22 visit.

Patients who complete the Week 22 visit and do not wish to enter an extension safety study will be instructed to discontinue study drug. Patients should not discontinue study drug before all the Week 22 assessments are performed and the unblinded medical monitors confirm all the data required for the analysis of the primary endpoint have been collected and reported. The follow-up visit will be conducted 28 days after the last dose of study drug and will serve as the last study visit.

3.6 Study Termination by Sponsor

If the Sponsor/CRO, 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 (if required) and follow-up will be performed in compliance with applicable regulations and guidelines.

4 STUDY POPULATION

This study includes patients with cortisol-secreting adrenal adenomas or hyperplasia associated with DM/IGT and/or uncontrolled systolic 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.

4.1 Inclusion Criteria

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

1. Male or female, 18 to 80 years of age, inclusive.
2. Lack of cortisol suppression (>1.8 µg/dL serum cortisol with adequate dexamethasone levels) on either 1-mg overnight or 2-mg 48-hour DST during Screening.
3. Suppressed or low (≤15 pg/mL) early-morning ACTH levels on at least 2 occasions during Screening.
4. A radiologically confirmed benign adrenal lesion (single adenoma, multiple adenomas, hyperplasia [≥3 times the size of the normal adrenal gland]) within 3 years prior to Screening.
5. 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).
   - Systolic hypertension (average SBP ≥130 to ≤170 mm Hg) based on 24-hour ABPM (Parati et al. 2014).
6. 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.
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 (average SBP >170 mm Hg or average DBP >110 mm Hg at Screening), based on 24-hour ABPM.
2. Has poorly controlled DM (HbA1c >12% at Screening).
3. Has DM Type 1.
4. Has abnormal liver test results (total bilirubin >1.5×ULN or elevated alanine aminotransferase or aspartate aminotransferase >3×ULN at Baseline).
5. Has severe renal insufficiency (glomerular filtration rate ≤29 mL/min/1.73 m^2 at Baseline).
6. Has uncontrolled, clinically significant hypothyroidism or hyperthyroidism.

7. 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).
8. Has persistent atrial fibrillation.
9. Has used or plans to use any treatments for Cushing syndrome within 12 weeks prior to Screening and throughout the study, including mifepristone, metyrapone, osilodrostat, ketoconazole, fluconazole, or any investigational drug for treatment of Cushing syndrome.
10. Patients who require inhaled glucocorticoids and have no alternative option if their condition deteriorates during the study.
11. Has adrenocortical carcinoma.
12. 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.
13. Has a history of cyclic Cushing syndrome with fluctuating clinical manifestations.
14. Has autonomous cosecretion of aldosterone.
15. Has plans for adrenalectomy or nodulectomy during the study, including follow-up.
16. Has taken any non-Cushing syndrome investigational drug within 4 weeks prior to Baseline, or within less than 5 times the drug's half-life, whichever is longer.
17. 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.
18. Ongoing use of any strong CYP3A4 inducer or any other prohibited medications (see Section 5.6).
19. Is pregnant or lactating.
20. Is a female patient of childbearing potential who cannot use a highly effective method of contraception (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); see Section 4.6.2.
21. Has an acute or unstable medical problem that could be aggravated by treatment with the investigational study drug.
22. Has a history of severe reaction to the study drug, to a similar class of drug, or to the study drug's excipient.
23. In the Investigator's opinion, should not participate in the study or may not be capable of following the study schedule.
24. Has known HIV, hepatitis B, or hepatitis C infection and is taking medication for treatment of HIV, hepatitis B, or hepatitis C infection.
25. Has used mitotane prior to Baseline.

4.3 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but did not meet the eligibility criteria for the study and were not enrolled.

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

If a patient is rescreened, they must sign a new informed consent form (ICF) and be assigned a new screening ID each time.

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 reasonable attempts to retain the patient in the trial and to document the specific reason why consent is withdrawn.

- Patient must be discontinued from the study if the patient becomes pregnant (see Section 8.11).

Patients should be discontinued from the study if the patient requires or starts a prohibited medication(s), or is not adhering to protocol procedures.

The Investigator can also withdraw patients from the study.

Reasons may include, but are not limited to:

- The Investigator decides it is in the patient's best interest to discontinue study drug and/or participation in the study.
- The patient experiences an AE or any of the special safety events outlined in Table 2, Section 5.4.1 that the Investigator believes requires withdrawal from the study.
- 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.

If a patient discontinues early from the study, the patient will complete an early termination (ET) visit at the time of last dose of study drug or within 2 weeks. They will be instructed to return to the site for the Week 22 visit per their original dosing schedule, and for the follow-up visit 28 days after the last dose of study drug. Depending on the timing of the patient's discontinuation, the visits may happen out of sequence, and either visit may serve as the patient's last study 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 5.4.

A patient may be withdrawn early from the study if the study is terminated early by the Sponsor or regulatory authority.

4.5 Replacement of Patients

Patients who withdraw from study early will not be replaced.

4.6 Restrictions During Study

4.6.1 Dietary Restrictions

The assigned dose will be administered orally once daily in the morning or at bedtime, 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.

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 childbearing 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 Surgery during the Study

Patients may not undergo unilateral or bilateral adrenalectomy or nodulectomy from Screening through the follow-up visit.

5 STUDY TREATMENTS AND MANAGEMENT

5.1 Study Drug and Placebo

Study drug is defined as relacorilant or placebo equivalent.

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

Table 1 Study Drug and Placebo: Description, 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, 28-count in child-resistant, blister-packaged cards and labeled per country requirement.	Capsules, 28-count in child-resistant, blister-packaged cards and labeled 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	4 capsules, once daily [a]	4 capsules, once daily [a]
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 11.6.

a. No matter which arm patients are randomized, every patient will take 4 capsules at each dose every day. The study drug is provided in a blister pack containing 28 capsules divided into 7 rows (Days 1 to 7). For patients randomized to relacorilant, each row will contain either a mix of relacorilant capsules and placebo capsules to ensure the patient gets the correct dose (i.e., for 300 mg of relacorilant, each row contains 3 relacorilant capsules and 1 placebo capsule), or the row will contain 4 relacorilant capsules (i.e., for 400 mg of relacorilant). For patients randomized to placebo, all 28 capsules in the blister pack contain placebo capsules. Patients must take all 4 capsules to ensure they get the full dose.

5.2 Non-Investigational Medicinal Agent

Not applicable.

5.3 Dose-Escalation Process

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 hyperglycemia and/or hypertension. The starting dose at Baseline will be 100 mg relacorilant or matching placebo 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 titrations after Week 18 are not permitted. Dose escalation will be performed based on tolerability assessed by the unblinded Medical Monitor considering the following factors (only in patients whose current dose is well tolerated).

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

- is ≥140 mg/dL or
- is <140 mg/dL and has not decreased by ≥30 mg/dL from Baseline

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

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

In patients with both DM/IGT and systolic hypertension:

- The 2-hour glucose of the oGTT:
- is ≥140 mg/dL or
- is <140 mg/dL and has not decreased by ≥30 mg/dL from Baseline

OR

The average 24-hour systolic BP (based on ABPM):

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

Dose escalation may be held if the patient cannot safely tolerate escalation to the next dose.

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.

Results of 2-hour oGTT, ABPM, and safety laboratory results will be reviewed by an unblinded Medical Monitor to monitor patient safety and allow dose escalation. The unblinded Medical Monitor will be unblinded to results of study assessments but is blinded to the treatment assignment. The Sponsor or designee, the Investigator, the blinded Medical Monitor, study-site personnel, and the patient will be blinded to treatment assignment (see Section 5.8).

5.4 Dose Modifications

Every effort should be made to administer study drug on the planned dose and schedule. However, if in the opinion of the Investigator a relacorilant dose is not tolerated, a dose interruption or dose reduction is permitted. Re-escalation after a dose reduction is permitted, with the approval of the Medical Monitor.

Dose reductions to manage excessive GR antagonism are detailed in Section 5.4.2.

Dose interruption or dose reduction to a previous dose may occur at any time.

During study-drug interruptions, patients will continue on the same visit schedule.

5.4.1 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, weight loss, nausea, vomiting, or muscle aches. Because relacorilant does not affect the MR, 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 (4–10 mg dexamethasone intramuscularly or intravenously for 2–3 days as needed)
- Investigator contact information.

Table 2 Criteria for Dose Modification or Discontinuation Due to Special Safety Events

	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 (4–10 mg), followed by additional parenteral or oral doses once or twice daily for 1–3 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 MR 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 highest dose previously tolerated by 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; MR, mineralocorticoid receptor.
a. For the purpose of this assessment, nausea and vomiting are considered 1 criterion.

5.4.2 Pharmacokinetic Criteria for Dose Adjustment or Discontinuation

Not applicable.

5.5 Concomitant Medications

Concomitant medications are defined as any prescription or over-the-counter medication, herbal preparations, and vitamin and/or mineral supplements that the patient began or continued in the period starting with the first dose of study 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.

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 syndrome, diabetes, and/or hypertension.

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 are prohibited. Strong CYP3A4 inducers are also prohibited. For example, the FDA provides a current list of Substrates 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 and inducers of CYP3A worldwide. The Investigator should contact the Medical Monitor with any questions.

Patients on such medications at Screening will need to have their dose adjusted or be switched to an alternative medication. For patients switched to an alternative antidiabetic or antihypertensive medication, there must have been no increase in medication dosage for at least 4 weeks prior to first dose of study medication (see Table 3).

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.

Permitted concomitant medications are listed in Table 3.

Table 3 Permitted Concomitant Medications

Medication	Use and/or Restriction
Mineralocorticoid receptor antagonists and other potassium-sparing diuretics	Do not initiate or increase dose without prior consultation with the Medical Monitor.
Potassium supplements	To treat hypokalemia
Insulin and oral antidiabetic medication	Do not take before the oGTT on the day of the procedure; can be taken with food after oGTT is completed Dose can be decreased during study-drug dosing to prevent hypoglycemia; upward titration should be avoided and may occur only after consultation with the Medical Monitor.
Long-acting insulin	Can take the night before the oGTT.
Antihypertensive medication	Dose can be decreased during the study-drug dosing to prevent hypotension or orthostatic symptoms. Do not increase dose or add new antihypertensive medications without prior consultation with the Medical Monitor.
Lipid-lowering drug	No increases in current dose allowed from 4 weeks before Baseline through the follow-up visit.

oGTT, oral glucose tolerance test.

5.5.1 Rules for Use of Antidiabetic and Antihypertensive Concomitant Medications

- Patients should not take antidiabetic medications before the oGTT on the day of the procedure; antidiabetic medications may be taken with food after the oGTT is completed. Long-acting insulin may be taken the prior evening.
- If any modification of existing diabetes medications or initiation of new diabetes medication is being considered during dosing, a 2-hour oGTT glucose should be obtained prior to modification of medications.
- Unblinding of fasting or postprandial glucose from the 2-hour oGTT or 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 during dosing, an ABPM should be performed prior to modification of medications.

5.5.1.1 Decrease or Discontinuation of Concomitant Medications

In patients with DM/IGT at Baseline

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.

Every effort should be made to obtain an oGTT prior to a reduction in anti-diabetic medication (if patient's condition allows it).

The unblinded Medical Monitor will notify the site of the pre-challenge fasting or 2-hour glucose from the oGTT decreases below 70 mg/dL.

Unblinding of pre-challenge fasting or the 2-hour glucose of the oGTT will not result in the unblinding of study treatment.

In patients with uncontrolled systolic hypertension at Baseline

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.

Every attempt should be made to obtain an ABPM prior to any decrease of BP medication (if patient's condition allows it).

The unblinded Medical Monitor will notify the site if BP decreases below 100 mm Hg average SBP or 60 mm Hg mean diastolic by ABPM.

Unblinding of ABPM results will not result in the unblinding of study treatment.

5.5.1.2 Increase or Initiation of Concomitant Medication

In patients with DM/IGT at Baseline

Increases in, or initiation of, antidiabetic medications used as rescue medication are allowed if patients meet one of the following criteria:

Local laboratory based on standard of care assessments (serum glucose and/or HbA1c):

- Morning fasting glucose >300 mg/dL on ≥2 consecutive days
- HbA1c >12%

Central laboratory study related assessments (serum glucose, HbA1c and/or 2-hour oGTT):

Results will be reviewed by an unblinded Medical Monitor to monitor patient safety. If a patient meets at least 1 of the following criteria, the results will be communicated to the study site, and rescue medication may be initiated or increased.

- Morning OR pre-challenge fasting glucose from the 2-hour oGTT >300 mg/dL
- HbA1c >12%
- Pre-challenge fasting glucose increases by 50 mg/dL AND the 2-hour oGTT glucose increases by 100 mg/dL from Baseline

If antidiabetic medication dose is increased or medication is initiated during the study, oGTT and HbA1c tests will be performed per the protocol schedule.

In patients with uncontrolled systolic hypertension at Baseline:

Increases in, or initiation of, antihypertensive medications used as rescue medication are allowed if patients meet one of the following criteria (based on standard-of-care measurements):

- Mean office SBP >170 mm Hg or DBP >110 mm Hg on ≥3 measurements obtained 15 minutes apart
- Average SBP >170 mm Hg or DBP >110 mm Hg based on standard of care ABPM

Study ABPM results 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:

- Average SBP >170 mm Hg or DBP >110 mm Hg

Unblinding of ABPM results will not result in the unblinding of study treatment.

If antihypertensive medication dose is increased or medication is initiated during the study, ABPM tests will be performed per regular schedule.

5.6 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.
- Mifepristone.
- Strong CYP3A4 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 glucocorticoids (with the 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.

5.7 Method of Treatment Assignment and Randomization

Eligible patients will be randomized 1:1 to relacorilant or placebo and stratified by one factor (disease at Baseline) with 3 levels:

- DM/IGT only at Baseline
- Systolic hypertension only at Baseline
- DM/IGT and systolic hypertension at Baseline

Randomization will be centrally assigned using [redacted]. The log-in information and directions for the [redacted] will be provided to each site.

Study drug will be dispensed at the study visits summarized in 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.

5.8 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) that could potentially reveal the treatment assignment in some patients 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 emergency unblinding toll-free number, which can be found in the study manual. The Investigator should notify the Sponsor of any unblinding occurrences.

[redacted]

[redacted]

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

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

Note: Even if laboratory 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.

5.9 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.

5.10 Product Accountability and Treatment Adherence

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.

After study drug accountability monitoring has occurred, opened and unopened cartons of study drug must be returned to the Sponsor or its designee at the end of the study or destroyed onsite upon approval from Sponsor, 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.

5.11 Continued Access to Study Treatment

All patients completing the study will be eligible to enter an extension study provided that they have at least 80% adherence with scheduled dosing (by capsule counts).

5.12 External Data Review Committee

5.12.1 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 and actions taken will be documented in meeting minutes.

5.13 Monitoring of and Treatment for Electrolyte Abnormalities and Edema

Monitoring for electrolyte abnormalities occurs at every visit and any clinically significant abnormality should be treated per standard of care.

Monitoring for edema occurs at every visit during a physical examination and should be treated per standard of care.

6 DESCRIPTION OF STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in Appendix A. Protocol waivers or exemptions are not allowed.

The Investigator and Sponsor will conduct the study in accordance with ICH Good Clinical Practice (GCP) and local regulations. Adherence to the study-design requirements is essential and required for study conduct, and the Investigator must ensure that trial 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 SoA.

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

Written informed consent must be obtained before initiating any study-mandated procedures. If allowed by local regulatory authority, remote consenting will be permitted if access of patients to the study site is restricted due to the COVID-19 pandemic. IRB/EC guidelines should be followed.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria.

6.1.1 Dexamethasone Suppression Test

The dexamethasone suppression test (DST) will be performed at Screening. Dexamethasone will be administered either as a 1-mg (or higher) dose overnight or a 2-mg dose over 48 hours; a blood sample will be drawn and will be tested at a central laboratory. In special circumstances pre-approved by the Sponsor, a blood sample may be tested at a local laboratory. Dexamethasone levels should be measured concurrently.

Estrogen preparations that affect significantly the cortisol binding globulin levels, including birth control and hormone replacement treatments, should be held for a duration of at least 5 half-lives of the estrogen analogue prior to DST.

6.1.2 Adrenal-Imaging History

Confirmation of a benign adrenal lesion can be made from the most recent imaging obtained as part of standard of care (within three years prior to Screening).

If the imaging report or the actual imaging study is not available, an adrenal imaging study should be performed to confirm study eligibility before dosing with study drug.

6.1.3 History Cushing-Syndrome–Medication Washout

Medications used in the treatment of hypercortisolism are prohibited and require washout of at least 12 weeks before Screening. Patients requiring washout of a medication for Cushing

syndrome must complete the Screening/Baseline oGTT, HbA1c, and 24-hour ABPM after washout and within 2 weeks before Day 1 dosing.

6.1.4 Demographics and Baseline Disease Characteristics

Patient demographic data, including age at time of informed consent, sex, and race/ethnicity, and baseline disease characteristics, such as years since diagnosis of hypercortisolism (e.g., primary pigmented nodular adrenocortical disease, primary macronodular adrenal hyperplasia, adrenal adenoma), will be documented.

6.1.5 Medical and Medication History

Relevant patient medical history, including the diagnosis, etiology, and treatment history of hypercortisolism (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). Adrenal surgical 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 to treat hypercortisolism, diabetes, and/or hypertension taken in the 3 months prior to Day 1.

6.2 Safety Assessments

Safety will be determined from evaluation of AEs, physical examinations, clinical laboratory tests, vital signs, and ECGs.

6.2.1 Physical Examination

A comprehensive physical examination will be performed. If clinically significant abnormalities are observed during Screening, they should be reported in the patient's medical history; if observed any time after the first dose of study drug (Day 1), they will be considered treatment-emergent AEs.

Investigators will assess the general physical appearance of patients during the examination.

6.2.2 Vital Signs

Vital signs, including BP, heart rate, respiratory rate, and 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 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.

To determine whether an increase in or initiation of antihypertensive medication is needed for patients with hypertension, office blood pressure measurements may be collected. At least three

blood pressure measurements separated by an interval of 15 minutes in the designated arm are required. If 2 sequential readings differ by >5 mm Hg (systolic or diastolic), repeat the measurement until consecutive readings are within 5 mm Hg of each other.

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.

6.2.3 Height, 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.

Body weight, measured without overcoat and shoes and with only light clothing, will be measured at every visit.

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

6.2.4 Electrocardiogram

Twelve-lead ECG tracings will be obtained from all patients in duplicate at the visits noted in Appendix A. Patients should lie down for ≥10 minutes before each ECG evaluation.

On days when study drug is administered, the ECG should be performed 2 hours (±30 minutes) after study-drug dosing. 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, duplicate ECG recordings should be obtained. The final decision to exclude 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.

Electrocardiogram data will be submitted to a central reviewer; instruction will be provided in the study manual.

6.2.5 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 consistent with the current Investigator's Brochure for relacorilant.

6.2.6 Concomitant Medications

Review usage and dosage of antidiabetic and antihypertensive medications. See Section 5.4 and Section 5.5 for rules for use of antidiabetic and antihypertensive concomitant medications and the procedures to accompany any changes.

6.2.7 Clinical Laboratory Assessments

6.2.7.1 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.

During Screening, the Investigator will review laboratory reports evaluate the results, and sign/date the report.

During dosing, all laboratory assessments will remain blinded. The unblinded Medical Monitor will review laboratory values and notify the Investigator and study-site staff of any significant out-of-range laboratory values. Critical lab values will be reported directly by the central lab to the Investigator. The unblinded Medical Monitor will follow up with the site to discuss critical laboratory values. To maintain the blind, investigators should not repeat laboratory tests locally unless medically necessary.

Any clinically significant laboratory value will be reported as an AE by the Investigator. Patients with a clinically significant out-of-range laboratory value will be followed until the laboratory value returns to normal or becomes medically stable. The Investigator will treat the patient, as medically required, at appropriate intervals until this occurs.

Laboratory tests to be performed are listed in Table 4 and should be performed according to the schedule provided in Appendix A.

Table 4 Clinical Laboratory Variables Evaluated During the Study

Hematology	**Serum Chemistry**	**Glucocorticoid-Receptor Activity**
Red blood cell count	Sodium	Potential biomarkers of GR activity
Hemoglobin	Potassium	**Pregnancy**
Hematocrit	Calcium	Serum/urine pregnancy test
Mean corpuscular hemoglobin	Chloride	**Thyroid Function**
Mean corpuscular hemoglobin volume	Phosphorus	Thyroid-stimulating hormone
Mean corpuscular volume	Magnesium	Total T3 Reflex
Platelet count	Creatinine	Free T4 Reflex
Mean platelet volume	Creatine kinase	**Glucose Control**
Red-blood-cell distribution and width	Bilirubin (total and direct)	2-hour oGTT [b]
White-blood-cell count	Albumin	HbA1c
Neutrophils (percent and absolute)	Alkaline phosphatase	**Biochemical Markers for Bone Remodeling**
Lymphocytes (percent and absolute)	Lactate dehydrogenase	Serum osteocalcin
Monocytes (percent and absolute)	Aspartate aminotransferase	**Coagulation panel [a]**
Eosinophils (percent and absolute)	Alanine aminotransferase	Factor VIII
Basophils (percent and absolute)	Fasting glucose	von Willebrand factor
Pharmacokinetic	Fasting insulin	Protein S
Relacorilant	Blood urea nitrogen	Protein C
Pharmacodynamic	Uric acid	Thrombin antithrombin (TAT)
DST with dexamethasone levels	Bicarbonate	Partial thromboplastin time (PTT)
Urinary free cortisol (UFC)	Total protein	
Salivary cortisol	**Lipid-Metabolism Panel [a]**	
Hypothalamic-pituitary-adrenal (HPA)-axis parameters:	Total cholesterol	
Plasma ACTH	Low-density lipoprotein-cholesterol	
Serum DHEA-S	High-density lipoprotein-cholesterol	
Fasting serum cortisol	Very low-density lipoprotein cholesterol	
	Triglycerides	

ACTH, adrenocorticotropic hormone; DHEA-S, dehydroepiandrosterone sulfate; DST, dexamethasone suppression test; GR, glucocorticoid receptor; HbA1c, hemoglobin A_{1c}; oGTT, oral glucose tolerance test; T3, triiodothyronine; T4, thyroxine.

a. Lipid-metabolism panel and coagulation panels should be performed either before or ≥24 hours after DST.

b. 2-Hour oGTT includes glucose, insulin, and glucagon (at selected visits).

6.2.7.2 Sample Collection, Preparation, and Shipping

Instructions for collection, preparation, and shipping of all laboratory samples will be provided in the study laboratory manual.

Shipping instructions for samples collected for PK analysis and GR activity biomarkers will also be provided. Long-term retention of biological samples is described in Section 11.5.

6.2.7.3 Blood-Volume Summary

Blood samples will be used for analysis of safety laboratory, efficacy, PK, PD, biomarker, and pharmacogenetic parameters. The total volume of blood to be collected from each patient will be no more than 505 mL for his/her entire study participation.

6.3 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 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, as specified in Appendix A.

6.4 Efficacy Assessments

The key efficacy assessments in this study are effects on glucose tolerance in the impaired glucose tolerance/diabetes subgroup and the effects on BP in the hypertensive subgroup. All other effects assessments are considered exploratory. Table 5 lists all efficacy assessments. Details are provided below.

Table 5 List of Efficacy Assessments

$AUC_{glucose}$	Reduction in concomitant medications for DM or hypertension
Glycated hemoglobin (HbA1c) concentration	Systolic blood pressure (based on ABPM)
Fasting glucose	Diastolic blood pressure (Based on ABPM)
Fasting insulin	Hormonal and menstrual cycle
2-hour oGTT glucose, insulin, and glucagon (glucagon at select timepoints)	Serum osteocalcin
Plasma ACTH	Bone density
Serum DHEA-S	Trabecular bone score
Fasting serum cortisol	Body composition
Late-night salivary cortisol	Factor VIII
Early-morning salivary cortisol	von Willebrand factor
Beck Depression Inventory	Protein S
Cushing QoL questionnaire	Protein C
Sit-to-stand test	Thrombin antithrombin (TAT)
Trail-making test	Partial thromboplastin time (PTT)

6.4.1 Glucose Tolerance

A 2-hour oGTT will be used to assess the effect of study drug on glucose tolerance, insulin resistance indices, and hyperglucagonemia ($AUC_{insulin}$, Matsuda Index, HOMA IR, and at selected visits $AUC_{glucagon}$) following an 8-hour fast at the time points specified in Table 11.

In general, patients should not take antidiabetic oral medication or insulin the morning of their visit, however, long-acting insulin can be taken the night before. Oral antidiabetes medications and insulin preparations can be taken with food after completion of the oGTT.

During the 2-hour oGTT, blood samples for plasma glucose, insulin, and glucagon will be collected before the glucose drink and 0.5, 1.0, 1.5, and 2.0 hours after the glucose drink (see Table 6).

In patients with an increase to their DM medications before or during Screening, oGTT should be performed ≥4 weeks after the increase in the diabetes medication and within 2 weeks prior to the Baseline Visit. oGTT during Screening should be performed either before, or ≥24 hours after, the DST test.

Table 6 Time Window for Collection of 2-hour oGTT Blood Samples

Nominal Time	Reporting Standards
0.5, 1.0, 1.5, and 2.0 hours post glucose drink	±10 minutes

6.4.2 Ambulatory Blood Pressure Monitoring (ABPM)

The 24-hour ABPM will be assessed for patients with an increase to their anti-hypertension medications either before or during Screening, ABPM should be performed ≥4 weeks after the increase and within 2 weeks prior to the Baseline Visit. ABPM during Screening should be performed either before, or ≥24 hours after, the DST test. At least 2 attempts should be made to obtain an accurate ABPM in all patients enrolled in the study.

Average 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) at the time points specified in Appendix A. The patient should use the monitor during a time when a full 24-hour recording can be completed. The patient should perform the ABPM under consistent conditions throughout the study. In cases where the ABPM fails QC and needs to be repeated, initiation of the ABPM at home will be allowed. The monitor should be worn on the non-dominant arm. Please see the vendor manual for additional details.

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 with the exception of the Week 22 Visit where the ABPM should be performed within 7 days prior to the visit. If more than 2 consecutive hours, or 5 hours over the entire period are missing, then the data are considered missing, and test should be repeated. The results of 24-hour ABPM will remain blinded.

Standard-of-care ABPM may be performed as needed in the opinion of the Investigator.

6.4.3 Glycated Hemoglobin (HbA1c)

Blood samples will be collected to measure HbA1c, a glycoprotein whose concentration reflects the amount of glucose bound to hemoglobin. In patients who have an increase to their DM medications before or during Screening, HbA1c, should be performed ≥4 weeks after the increase in diabetes medication and within 2 weeks prior to the Baseline Visit.

6.4.4 Hypothalamic-Pituitary-Adrenal Axis Parameters

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

6.4.4.1 Plasma ACTH

Plasma ACTH should be measured at least twice during Screening. ACTH should be measured either before, or at least 24 hours after, the DST test.

6.4.4.2 Plasma DHEA-S

Plasma DHEA-S should be measured either before, or at least 24 hours after, the DST test.

6.4.4.3 Fasting Serum Cortisol

Serum fasting cortisol should be measured along with ACTH either before, or at least 24 hours after, the DST test.

6.4.5 Sit-to-Stand Test

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 same or similar chair should be used for all measurements.

The study staff will use a stopwatch to measure the total time it takes for the patient to stand up and sit down 5 consecutive 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.

6.4.6 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 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.

6.4.7 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.

6.4.8 DXA Scans

Trabecular bone score, bone mineral density, and body composition (change in the percent and absolute amounts of total body and regional fat and lean tissue [whole body, trunk, and leg)] will be determined from the DXA scans (Shepherd et al. 2017, Athimulam et al. 2019) for all patients, at the time points specified in Appendix A.

6.5 Pharmacodynamic Assessments

Samples for pharmacodynamic (PD) assessments will be collected from all patients at the time points specified in Appendix A.

6.5.1 Urinary Free Cortisol (UFC)

The 24-hour UFC with creatinine test will be collected by the patient at home 2 times during Screening only. 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.

Test must be performed either before or ≥24 hours after DST test.

Patients 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.

6.5.2 Late-Night Salivary Cortisol

During Screening, two late-night salivary cortisol samples will be collected, one of which will be the night before the Day 1/Baseline Visit. Tests should be performed either before, or ≥24 hours after, the DST test.

During treatment with study drug, a late-night salivary-cortisol sample should be collected at the patient's home at bedtime the night before the 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 and they will be given supplies for the collection of saliva.

6.5.3 Early-Morning Salivary Cortisol

Early-morning salivary cortisol will be collected at the site if the patient arrives before 9 am (to avoid mix up with the late-night salivary cortisol samples collected by the patient). If the visit is scheduled after 9 am, the sample will be collected at home by the patient the morning of the visit. Early-morning salivary cortisol should be collected either on the same day as the late-night salivary cortisol is collected, or the morning after.

6.6 Patient-Reported Outcomes

6.6.1 Cushing QoL 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 (Nelson et al. 2013). Lower values reflect lower quality of life.

6.6.2 Beck Depression Inventory-II

The Beck Depression Inventory-II (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 0–63. Scores of 0–13 indicate minimal depression, 14–19; mild depression; 20–28; moderate depression; 29–63; severe depression.

6.7 Pharmacokinetic (PK) Assessments

Intensive PK sampling to assess the plasma concentrations of relacorilant and/or its metabolites will be conducted in all patients at the Week 18 visit (Appendix A).

Pharmacokinetic sampling will take precedence over other procedures when more than 1 procedure is scheduled for the same time point relative to dosing.

PK sampling should be performed on the ongoing dose, prior to any dose escalation.

Acceptable time windows for PK samples are shown in Table 7.

Table 7 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

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

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel.

6.8 Pharmacodynamic/Biomarker Assessments

Blood samples will be obtained from all patients for analysis of mRNA expression of glucocorticoid-modulated genes and proteins at the time points specified in Appendix A. Test must be performed either before or ≥24 hours after DST test. The results of these assessments will remain blinded.

6.9 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.

6.10 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 11.5. 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 Activities (SOA) 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 and reported to the IRB/EC as applicable. 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

The window for each study visit is relative to the Baseline Visit. The acceptable visit window is ±7 days for all visits (except for the Week 22 and ET visits, in which case a 3-week visit window [2 weeks before the scheduled visit, 1 week after the scheduled visit] and 2-week [2 weeks after the scheduled visit] visit window, respectively, is permitted).

Patients will remain on study treatment post Week 22 visit until it has been confirmed that all results for efficacy assessment have been received and no repeat assessments are required. The follow-up visit must occur 28 days after the last dose of study drug.

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 after completion of all predose procedures.
- All clinical laboratory samples and the predose PK samples will be collected when the patient is fasting (at least 4 hours).
- Measurement of vital signs and ECG recordings should be avoided within 15 minutes after venipuncture or cannulation and, therefore, will normally be performed before blood sampling.
- At all visits beginning with Week 2, study drug should be taken in the clinic during the visit and after initial blood draws.
- At every visit during dose escalation (Week 2+) and maintenance phase (Week 14+), blood chemistry including potassium concentrations are checked, blood pressure is measured, and physical examination (including checking for edema) is conducted. Investigators are required to report adverse events to the Sponsor promptly.

- Pharmacokinetic sampling (at Week 18) 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 are:

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

- Ambulatory BP monitoring will be initiated in the clinic after all blood samples are obtained with the exception of the Week 22 Visit where the ABPM should be performed within 7 days prior to the visit.
- Study-drug dosing should occur after completion of the 2-hour oGTT (except for Week 18, when oGTT may take place after dosing for logistical issues due to intensive 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

- Electrocardiogram recording should be performed 2 hours ±30 minutes after study-drug dosing.

If a patient discontinues early from the study, the patient will complete an early termination (ET) visit at the time of last dose of study drug or within 2 weeks. They will be instructed to return to the site for the Week 22 visit per their original dosing schedule, and for the follow-up visit 28 days after the last dose of study drug. Depending on the timing of the patient's discontinuation, the visits may happen out of sequence, and either visit may serve as the patient's last study visit.

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 Clinical Assessments 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
- 12-lead ECG (in duplicate)

- Measure vital signs
- Review concomitant medications
- Draw blood samples for laboratory tests
  - Serum pregnancy test (women of childbearing potential only).
  - Chemistry and hematology
  - GR-activity biomarker test
  - 2-hour oGTT (after an 8-hour fast); should be collected ≥4 weeks after an increase in diabetes medication must be performed within 2 weeks of the Baseline Visit and used as Baseline
  - HbA1c (should be collected ≥4 weeks after an increase in diabetes medication); must be performed within 2 weeks of the Baseline Visit and used as Baseline
  - HPA-axis parameters
- Thyroid-function tests
- 24-hour UFC with creatinine (collected by the patient at home twice during Screening).
- DST with dexamethasone levels. 1-mg overnight or 2 day low-dose dexamethasone suppression test must be performed during Screening. Dexamethasone levels must be measured concurrently. Estrogen preparations, including birth control and hormone replacement treatments, should be held for a duration of at least 5 half-lives of the estrogen analogue prior to DST.
- Late-night salivary cortisol (collected by the patient at home at least twice on different nights during Screening), one of which will be the night before the Day 1/Baseline Visit).
- Early-morning salivary cortisol (collected at the site if the patient arrives before 9 am); should be collected either on the same day as the late-night salivary cortisol is collected, or the morning after.
- ABPM (24-hour) test will be assessed for all patients during Screening. For patients with an increase to their anti-hypertension medications either before or during Screening, ABPM should be performed ≥4 weeks after the increase. During Screening, ABPM should be performed either before, or ≥24 hours after, the DST test; must be performed within 2 weeks of the Baseline Visit and used as Baseline.
- Schedule next visit.

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

7.1.2 Baseline Visit (Day 1)

- 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, weight, and waist circumference
- Measure vital signs
- Review concomitant medications
- Urine pregnancy test (women of childbearing potential only)
- Draw blood samples for laboratory tests
  - Chemistry and hematology
  - Lipid-metabolism panel (fasting)
  - Coagulation panel
  - Serum osteocalcin
  - 2-hour oGTT, including measurement of glucagon levels (after an 8-hour fast and used as Baseline—unless performed within 2 weeks of the Baseline Visit; glucagon levels will be assessed only for patients with DM/IGT)
  - HbA1c (used for Baseline—unless collected within 2 weeks of the Baseline Visit)
- Early-morning salivary cortisol (collected at the site if the patient arrives before 9 am)
- Cushing QoL questionnaire
- Beck Depression Inventory
- Sit-to-stand test
- Trail-making test
- DXA scan (±2 weeks of the Baseline Visit); patients to get DXA scan before Baseline Visit only in the case they are already determined to qualify for the study
- Dosing diary
- Study-drug dispensing and/or adherence
- Query for AEs
- Schedule next visit

7.1.3 Week 2 (±7 days)

- Perform a complete physical examination, including, weight, and waist circumference
- Measure vital signs
- Query for AEs
- Review concomitant medications
- Urine pregnancy test (women of childbearing potential only)

- Draw blood samples for laboratory tests
  - Chemistry and hematology
  - 2-hour oGTT (after an 8-hour fast; for DM/IGT patients only)
- ABPM (24-hour) test (for hypertension patients only)
- Dosing diary
- Study-drug dispensing and/or adherence
- Schedule next visit

7.1.4 Week 6 (±7 days)

- Perform a complete physical examination, including, weight, and waist circumference
- Measure vital signs
- Query for AEs
- Review concomitant medications
- Urine pregnancy test (women of childbearing potential only)
- Draw blood samples for laboratory tests
  - Chemistry and hematology
  - GR-activity biomarker test
  - 2-hour oGTT (after an 8-hour fast; for patients with DM/IGT at Baseline)
  - HPA-axis parameters
- Late-night salivary cortisol (collected at the patient's home at bedtime the night before the study visit)
- Early-morning salivary cortisol (collected at the site if the patient arrives before 9 am)
- ABPM (24-hour) test (for patients with systolic hypertension at Baseline)
- Cushing QoL questionnaire
- Beck Depression Inventory
- Sit-to-stand test
- Trail-making test
- Dosing diary
- Study-drug dispensing and/or adherence
- Schedule next visit

7.1.5 Week 10 (±7 days)

- Perform a complete physical examination, including, weight, and waist circumference
- Measure vital signs
- Query for AEs
- Review concomitant medications
- Urine pregnancy test (women of childbearing potential only)
- Draw blood samples for laboratory tests
  - Chemistry and hematology
  - GR-activity biomarker test
  - 2-hour oGTT, including measurement of glucagon levels (after an 8-hour fast; for all patients; glucagon levels will be assessed only for patients with DM/IGT)
  - HbA1c (for all patients)
  - HPA-axis parameters
- Late-night salivary cortisol (collected at the patient's home at bedtime the night before the study visit)
- Early-morning salivary cortisol (collected at the site if the patient arrives before 9 am)
- ABPM (24-hour) test (for all patients)
- Cushing QoL questionnaire
- Beck Depression Inventory
- Sit-to-stand test
- Trail-making test
- Dosing diary
- Study-drug dispensing and/or adherence
- Schedule next visit

7.1.6 Week 14 (±7 days)

- Perform a complete physical examination, including, weight, and waist circumference
- Measure vital signs
- Query for AEs
- Review concomitant medications
- Urine pregnancy test (women of childbearing potential only)
- 12-lead ECG (in duplicate)

- Draw blood samples for laboratory tests
  - Chemistry and hematology
  - Coagulation panel
  - GR-activity biomarker test
  - 2-hour oGTT (after an 8-hour fast; for patients with DM/IGT at Baseline)
  - HPA-axis parameters
- Late-night salivary cortisol (collected at the patient's home at bedtime the night before the study visit)
- Early-morning salivary cortisol (collected at the site if the patient arrives before 9 am)
- ABPM (24-hour) test (for patients with systolic hypertension at Baseline).
- Cushing QoL questionnaire
- Beck Depression Inventory
- Sit-to-stand test
- Trail-making test
- Dosing diary
- Study-drug dispensing and/or adherence
- Schedule next visit

7.1.7 Week 18 (±7 days)

- Perform a complete physical examination, including, weight, and waist circumference
- Measure vital signs
- Query for AEs
- Review concomitant medications
- Urine pregnancy test (women of childbearing potential only)
- Draw blood samples for laboratory tests
  - Chemistry and hematology
  - 2-hour oGTT (after an 8-hour fast; for patients with DM/IGT at Baseline)
  - Intensive PK sampling
- Early-morning salivary cortisol (collected at the site if the patient arrives before 9 am)
- ABPM (24-hour) test (for patients with systolic hypertension at Baseline)
- Cushing QoL questionnaire
- Beck Depression Inventory

- Sit-to-stand test
- Trail-making test
- Dosing diary
- Study-drug dispensing and/or adherence
- Schedule next visit

7.1.8 Week 22 (-14/+7 days)

- 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
- Query for AEs
- Review concomitant medications
- 12-lead ECG (in duplicate)
- Urine pregnancy test (women of childbearing potential only)
- Draw blood samples for laboratory tests
  - Chemistry and hematology
  - Lipid-metabolism panel (fasting)
  - Coagulation panel
  - Serum osteocalcin
  - GR-activity biomarker test
  - 2-hour oGTT, including measurement of glucagon levels (after an 8-hour fast; for all patients; glucagon levels will be assessed only for patients with DM/IGT)
  - HbA1c (for all patients)
  - HPA-axis parameters
- Late-night salivary cortisol
- Early-morning salivary cortisol (collected at the site if the patient arrives before 9 am)
- ABPM (24-hour) test (for all patients), performed within 7 days prior to Week 22 Visit
- Cushing QoL questionnaire
- Beck Depression Inventory
- Sit-to-stand test
- Trail-making test

- DXA scan
- Study-drug dispensing* and drug adherence
- Schedule next visit

* Patients will remain on study treatment until it has been confirmed that all results for efficacy assessment have been received and no repeat assessments are required.

7.1.9 Early-Termination Visit (+14 days)

If the patient discontinues study drug prior to Week 22, the patient will be encouraged to complete the following assessments at the time of last dose of study drug or within 2 weeks. They will be instructed to return to the site for the Week 22 visit per their original dosing schedule, and for the follow-up visit 28 days after the last dose of study drug.

- Perform a complete physical examination, including, weight, and waist circumference
- Measure vital signs
- Query for AEs
- Review concomitant medications
- 12-lead ECG (in duplicate)
- Urine pregnancy test (women of childbearing potential only)
- Draw blood samples for laboratory tests
  - Chemistry and hematology
  - Lipid-metabolism panel (fasting)
  - Coagulation panel
  - Serum osteocalcin
  - GR-activity biomarker test
  - 2-hour oGTT, including measurement of glucagon levels (after an 8-hour fast; for all patients; glucagon levels will be assessed only for patients with DM/IGT)
  - HbA1c (for all patients)
  - HPA-axis parameters
- Late-night salivary cortisol
- Early-morning salivary cortisol (collected at the site if the patient arrives before 9 am)
- ABPM (24-hour) test (for all patients)
- Cushing QoL questionnaire
- Beck Depression Inventory
- Sit-to-stand test

- Trail-making test
- DXA scan (should not be repeated if it was already completed within 8 weeks prior to ET Visit; acceptable visit window is up to 3 months following ET Visit).
- Study-drug adherence
- Schedule next visit

7.1.10 Follow-Up Visit (±7 days)

- Perform a complete physical examination, including, weight, and waist circumference
- Measure vital signs
- Query for AEs
- Review concomitant medications
- Urine pregnancy test (women of childbearing potential only)
- Draw blood samples for laboratory tests
  - Chemistry and hematology
- Study-drug adherence

7.2 Unscheduled Visits

As appropriate, assessments deemed clinically necessary by the Investigator may be done 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. By exercising appropriate healthcare options, the Investigator remains responsible for managing AEs. All SAEs must be reported to Sponsor within 24 hours from awareness of the event.

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.

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. Sponsor or its designee will promptly evaluate all reported safety information against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators and applicable regulatory authorities.

8.2 Definition of an Adverse Event

An AE is any untoward medical occurrence in a study patient administered a pharmaceutical product that does not necessarily have to have a causal relationship with the 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 any study drug that emerges or worsens relative to the patient's pretreatment baseline, regardless of whether it is related to the study drug.

8.3 Definition of a Serious Adverse Event

An SAE is any AE resulting in any of the following outcomes:

- Death (i.e., the AE caused or led to the fatality)
- Life-threatening AE (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 that hypothetically might have caused death if it were more severe)
- Hospitalization or prolongation of existing hospitalization (i.e., hospitalizations for scheduled treatments and elective medical/surgical procedures are not SAEs by this criterion)
- Persistent or significant disability/incapacity (i.e., the AE results in substantial reduction of the patient's ability to perform activities of daily living)
- 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)
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such

medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

8.4 Expectedness

A serious AE is considered unexpected if not reported in the Investigator's Brochure or if the event is of greater severity or frequency than described in the Investigator's Brochure, (i.e., not specified in the RSI section of the Investigator's Brochure).

8.5 Clinical-Laboratory Adverse Events

All out-of-range laboratory values will be determined to be clinically significant or not clinically significant by the Investigator. An abnormal laboratory value that meets any of the following criteria will be recorded as an AE on the eCRF:

- Leads to a dose modification or patient withdrawal from the study.
- Is accompanied by clinical symptoms.
- Requires a change in concomitant medications.

Other clinically significant laboratory values may be reported as AEs at the discretion of the Investigator.

Patients with a clinically significant out-of-range laboratory value will be followed until the laboratory value returns to normal, the value becomes medically stable, or the patient is deemed by the Principal Investigator to be lost to follow-up. The Investigator will treat the patient as medically required at appropriate intervals until this occurs.

8.6 Documentation of Adverse Events

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

Collection of AEs will start immediately following signing of the ICF and will continue throughout the study. All AEs will be documented on the patient's medical record and AEs for all the randomized patients will be documented in the eCRF.

Illnesses present before the patient signs the informed consent form (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. AEs that occur after start of study treatment and up to and including 28 days after administration of the last dose of study drug will be considered TEAEs. Any AEs reported more than 28 days after the last dose of study drug will be considered posttreatment AEs and do not need to be reported to Corcept, unless the event meets the definition of serious (see Section 8.3) and the relationship to the study drug is possibly related, probably related, or related (see Section 8.7.2). In such cases, these posttreatment SAEs need to be reported per the process in Section 8.8 and are not to be entered in eCRF. 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 drug-related and unexpected (not specified in the RSI section of the Investigator's Brochure) or if the event is of greater severity or frequency than that described in the Investigator's Brochure) must be reported to the governing IRB/Independent Ethics Committee (IEC)/Health Authorities as required.

8.7 Adverse Event Classification

8.7.1 Intensity Grades of Adverse Events

Seriousness of an AE is not synonymous with severity. To describe the maximum severity of the AE on the AE eCRF, the Investigator will use the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 5.0 (NCI-CTCAE 2017). For events not listed in the NCI-CTCAE, the definitions from the NCI-CTCAE provided in Table 8 should be used to evaluate the grade of severity for the AE.

Table 8 AE 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

Source: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (NCI-CTCAE 2017).

8.7.2 Relationship of Adverse Event to Study Drug or Procedure

The Investigator responsible for the patient's care (or qualified designee) will assess causality of AEs and SAEs based on the causal attribution guidance in Table 9. The Investigator's assessment of causality must be provided for all AEs (serious and nonserious).

Table 9 Causal Attribution Guidance for AEs

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).
Related to study drug	An AE that is due to the use of the drug.

8.8 Procedures for Reporting a Serious Adverse Event

Any SAE occurring from the time of informed consent and for 28 days after the last dose of study drug must be reported immediately (latest within 24 hours) to the pharmacovigilance vendor by completing and submitting the SAE form to the contact specified 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.

8.9 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.10 Adverse Event Follow-Up

All AEs considered to be related to study drug (see Section 8.7.2) and all SAEs will be followed until resolution, until deemed stable by the 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 the Sponsor during the study and within 28 days of the last dose of study treatment.

8.11.1 Maternal Exposure

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

If any pregnancy occurs during the study or within 28 days of the final dose of the study drug, the Investigator or designee should inform the appropriate Sponsor representatives immediately but no later than 24 hours of when he or she becomes aware of it.

The Investigator or designee should 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) will, 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 study drug. For monitoring symptoms of excessive GR antagonism, refer to Section 5.4.1. If clinically significant GR antagonism is suspected, dexamethasone may be administered.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the patient.

8.13 Emergency Sponsor Contact

In a medical emergency (i.e., an event requiring immediate attention regarding the treatment of a patient, operation of the clinical study, and/or the use of study drug), 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 analysis populations are defined in Table 10.

Table 10 Definitions of Analysis Populations

Population	Description
Safety	All patients randomly assigned to study treatment and who take ≥1 dose of study treatment. Patients will be analyzed according to the treatment they actually received.
Intent-to-treat (ITT) [a]	The ITT population will include all patients who were randomized to receive relacorilant or placebo, even if they do not receive any study treatment. This population will be used for the analysis of the primary and secondary efficacy endpoints.
Modified intent-to-treat (mITT)	The mITT population will include all patients in the ITT population with ≥1 post-randomization efficacy assessment for the primary and secondary efficacy endpoints of ABPM and/or $AUC_{glucose}$. This population will be used for sensitivity analyses performed on the primary and secondary efficacy endpoints.
PK	The subset of the Safety population with adequate PK data.
PD	The subset of the Safety population with adequate PD data.

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

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 study unblinding.

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. If a Day 1 predose value is not available, the Screening measurement may be used as the baseline value.

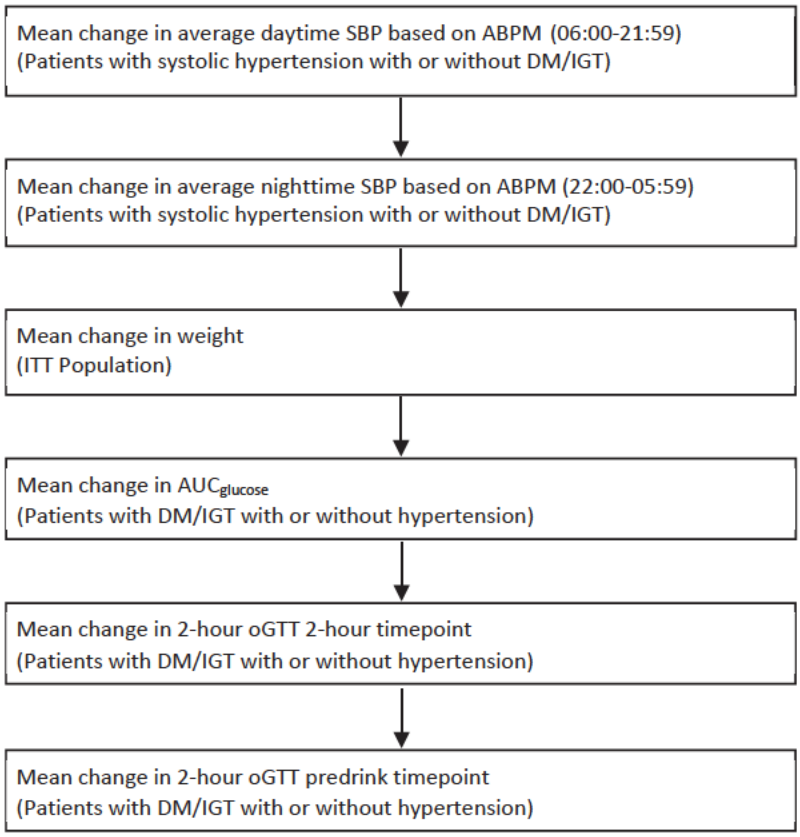
9.3 Hypothesis Testing

For the testing of the primary and certain secondary efficacy endpoints, adjustment for multiplicity will be implemented to maintain a 2-sided 0.05 significance level for the Family-Wise type I error rate.

In order to provide strong control of the Type I error, certain secondary analyses will be tested using a gated testing approach at a 2-sided alpha level of 0.05. If the null hypothesis is rejected

for the primary endpoint, certain secondary endpoints will be sequentially tested following the gatekeeping hierarchy (Figure 2). No adjustments for multiplicity will be made for other secondary or exploratory endpoints.

Figure 2 Sequential Gatekeeping Hierarchy



All statistical hypotheses for any other secondary endpoints and exploratory endpoints will be tested at a 2-sided 0.05 significance level unless otherwise specified.

9.4 Sample-Size Calculation

Approximately 130 patients are planned to be randomized into the study.

Attainment of the randomization targets within the DM/IGT and hypertension subgroups in this study assumes that 40% of randomized patients will have DM/IGT only, 40% will have hypertension only, and 20% will have both DM/IGT and hypertension. This projected sample size will result in randomization of approximately 78 patients with DM/IGT (with or without hypertension) and 78 patients with hypertension (with or without DM/IGT)

Seventy-eight patients with DM/IGT (39 patients per treatment group) will ensure at least 90% power to detect a difference of 3.1 h*mmol/L in mean changes in $AUC_{glucose}$ (based on the 2-hour oGTT measurement) between placebo and treatment arm. This calculation assumes a common standard deviation of 3.7 h*mmol/L, and a 0.025 two-sided significance level two-sample t-test. Twenty percent dropout rate from Baseline to Week 22 is assumed in this calculation.

Seventy-eight patients with hypertension (39 per treatment group) will ensure at least 90% power to detect a difference between placebo and treatment arms in average SBP of 7 mm Hg (based on ABPM). These calculations assume a common standard deviation of 8 mm Hg and a 0.025 two-sided significance level two-sample t-test. Twenty-eight percent dropout rate from Baseline to Week 22 is assumed in this calculation.

In summary, the expected randomization of 130 patients in the study will result in 78 patients within each of the DM/IGT and hypertension subgroups. This sample size will provide sufficient power to detect the target differences in the primary endpoint for each of the subgroups.

9.5 Analysis Plan

9.5.1 Patient Disposition

The numbers of patients who were enrolled, and who were randomized along with the reasons for withdrawal will be summarized by treatment group.

9.5.2 Demographic and Baseline Characteristics Data

Demographics and baseline characteristics will be summarized for the Safety Population, ITT, and mITT 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 adrenal adenomas/hyperplasia.

9.5.3 Prior and Concomitant Medications

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

9.5.4 Analysis of Efficacy Endpoints

9.5.4.1 Analysis of Primary Efficacy Endpoint

The primary endpoint is defined in Section 3.2.1.

For the hypertension subgroup of the ITT Population, the estimand of interest is the between-treatment difference in change in average SBP based on 24-hour ABPM from Randomization to Week 22 (estimated using a MMRM model) regardless of treatment discontinuation and as if rescue medication was not available. For the primary analysis, missing values at Week 22 for patients who use rescue medication or discontinue treatment early, will be imputed using a placebo wash-out multiple imputation. For those patients who use rescue medication for hypertension after randomization and before Visit Week 22, the values collected after first use of rescue medication are irrelevant to the clinical question of interest and will not be used in the analysis. For patients who discontinue treatment early, all collected values (including retrieved drop-outs) will be used in the analysis. Additional details are provided in the SAP.The primary efficacy analysis for the primary endpoint of change in 24- hour average SBP from Randomization to Week 22 will be performed using a linear mixed-model-for-repeated-measures

(MMRM) using data with the imputation method described above. Restricted maximum likelihood (REML) estimation will be used. The MMRM model will include Baseline average SBP based on 24-hour ABPM as a covariate; treatment, visit, and treatment by visit interaction, and stratification factor as fixed effects; patients within treatment groups as random effects. In the hypertension subgroup, the stratification factor at randomization identifies patients with or without DM/IGT. 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.

The primary analysis will determine whether there is a difference between treatment groups in terms of change in 24-hour average SBP from Randomization to Week 22. This will be accomplished by using appropriate linear contrasts of the parameters in the MMRM model described above.

Additional sensitivity and supplemental analyses for the primary endpoint, including subgroups of interest, will be specified in the SAP.

9.5.4.2 Analysis of Secondary Efficacy Endpoints

The secondary efficacy endpoints are defined in Section 3.2.2.

For continuous endpoints in 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 Baseline value (for the respective endpoint) as a covariate; treatment, visit, treatment by visit interaction, and stratification factor (at randomization) 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.

The analysis for each of the endpoints will determine whether there is a difference between treatment groups in terms of change from Randomization to Week 22. 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 endpoints described as proportions in the study, the point estimate and the 2-sided 95% CI will be calculated. A logistic model including effects for treatment, continuous baseline value, and stratification factor at randomization will be used to assess differences in proportions between treatment arms (Steingrimsson et al. 2017).

9.5.4.3 Analysis of Exploratory Endpoints

The Exploratory Endpoints listed in Section 3.2.3 will be analyzed using methods similar to the analyses of primary and secondary endpoints if they are measured repeatedly over the course of the study. Detailed analysis methods will be described in SAP.

9.5.5 Safety Analyses

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

TEAEs will be summarized by treatment group. Serious AEs and TEAEs that lead to study-drug withdrawal or withdrawal from the study will be summarized by treatment group and listed by patient.

TEAEs will be summarized by 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.

Clinical laboratory test results (chemistry and hematology), vital sign measurements, and ECG interval results will be summarized as changes from baseline by parameter and visit using descriptive statistics. Shift tables will describe changes from Baseline in clinical laboratory values.

9.5.6 PK Analysis

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

9.5.7 PD Analysis

Analysis of PD endpoints will be described in a separate PD analysis plan finalized before study unblinding.

9.5.8 Biomarker/Pharmacogenetic Analysis

Biomarker and pharmacogenetic exploratory analyses will be described in the SAP finalized before study unblinding.

9.5.9 Interim Analysis

Not applicable.

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 CFR Part 56.103), IEC regulations, or applicable local regulations. The protocol, informed consent form(s) (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 consent form 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/IEC on receipt of amendments and annually, as local regulations require.

The investigators should not implement any deviation form, or changes to, the protocol without agreement by Corcept and documented approval from IRB/IEC, except where necessary to eliminate an immediate hazard(s) to trial subjects.

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

The Sponsor or their designee 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 the Sponsor or their designee.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB/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 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 and/or from the patient's legally authorized representative prior to enrollment into the study or conducting any study procedures.

The Investigator(s) at each center will ensure that each 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 Informed Consent process discussion should be documented in patient's record. 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.

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

The ICF should include information about the possible retention of biological samples at the conclusion of this study. With the patient's permission:

- Samples, including blood, plasma, serum and tissue samples, may be retained for future analysis to help identify biomarkers of disease or relacorilant treatment.
- Samples may be retained for future determination of active metabolite concentrations and possible biomarkers related to drug response.

10.3.2 Patient Confidentiality

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

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 or its designee, regulatory agencies, and IRB/IEC/Research Ethics Board (REB). 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 or, if appropriate, the patient's legally authorized representative. If permission to use protected health information is withdrawn, it is the Investigator's responsibility to obtain a written request, to ensure no further data will be collected from the patient, and the patient will be removed from the study.

Written authorization is to be obtained from each patient before enrollment into the study, and/or from the patient's legally authorized representative in accordance with the applicable privacy requirements.

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Study Monitoring

Monitoring of the study site (including, but not limited to, reviewing CRFs for accuracy and completeness, and assessing compliance with the protocol and adherence to regulatory and GCP requirements) will be performed by the Sponsor's Clinical Monitor or designee.

- Monitoring will be performed in accordance with applicable local and country regulations and guidance.
- Monitoring will include regular site visits and communication with the Investigator and site staff as appropriate to discuss and answer study questions; ensure compliance with the protocol; and ensure quality and integrity of the data.
- Monitors will ensure the site maintains an adequate supply of study drugs; any necessary supplies and ensure that appropriate storage conditions are maintained.
- Monitoring visits will be conducted according to the US CFR Title 21 parts 50, 56, and 312; and International Council on Harmonisation (ICH) Guideline for GCP.

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

11.2 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 (QA) audit during the study by the Sponsor or its designee on behalf of the Sponsor. 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 that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, 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).

The investigator site will provide direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

11.3 Documentation

11.3.1 Case Report Forms and Study Records

The Investigator must generate and maintain complete, adequate, accurate, reliable, and consistent records to enable full documentation of study conduct. Study data will be captured on CRFs. 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 Access to Source Documentation

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

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

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

11.3.3 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. Examples of these original documents and data records include, but are not limited to, a patient's medical records, hospital charts, clinic charts, the Investigator's patient study files, as well as the results of diagnostic tests such as x-rays, laboratory tests, and ECGs. All data entered into the CRFs must be substantiated by a source document.

11.3.4 Study Files and Retention of Study Records

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 documents 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. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

Patient identification codes (patient names and corresponding study numbers) will be retained for this same period of time. 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. The Investigator or designee must contact the Sponsor before disposing of any study records.

11.4 Sample Collection, Preparation, and Shipping

Instructions for collection, preparation, and shipping of all laboratory samples will be provided in the study laboratory manual.

11.5 Long-Term Retention of Biological Samples

All biological samples will be retained by Corcept or designee under the original informed consent of the patient and the IRB/IEC approval. Samples will be held for a period up to 20 years after acquisition. Corcept or the 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 his/her samples used for future research at any time without affecting their participation in the study or their care by the health provider. Upon receipt of a request for sample destruction, that patient's sample(s) will then no longer be used for research purposes, 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 labelled in accordance with trial procedures to comply with all applicable laws, which may include but are not limited to European Directives 95/46/EC and 2002/58/EC 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. 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 and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act and the 2006 Human Tissue (Scotland) Act.

11.6 Clinical Supplies

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

11.6.2 Clinical-Supply Inventory

A detailed inventory must be completed 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 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 designee must provide an explanation for any destroyed or missing study drug or study materials.

The Investigator or 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 designee must retain all unused or expired study supplies until the study monitor (on-site CRA) has confirmed the accountability data and Sponsor has approved return or destruction.

11.6.3 Return or Disposal of Study Drug and/or Supplies

All clinical study drug and/or supplies will either be destroyed by the site per institutional policy, or be returned to the Sponsor or designee for destruction.

Unused study drug 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.

Documentation must be provided to the Sponsor and retained in the Investigator study files. If a site is unable to destroy study drug appropriately, the site can return unused study drug to the Sponsor upon request. The return of study drug or study-drug materials must be accounted for on a Study-drug Return Form provided by the Sponsor.

11.7 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 or destroyed study product.

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

At the end of the study, after final drug inventory reconciliation by the study monitor, the study site will dispose of and/or destroy all unused investigational medicinal product supplies, including empty containers, according to SOPs.

11.8 Post-Trial Care

Patients who successfully complete the clinical study will be permitted to continue relacorilant treatment in an extension study provided they have at least 80% adherence with scheduled dosing (by capsule counts).

Patients who enroll in an extension study without interruption will not be required to complete the follow-up visit. The last study visit for these patients will be the Week 22 visit.

11.9 Protocol Noncompliance

Prospective approval of deviations from the inclusion and exclusion criteria, also known as protocol waivers or exemptions, is not permitted.

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or manual of procedures (MOP) requirements. The noncompliance may be either on the part of the patient, the Investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. These practices are consistent with ICH E6.

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

Such contact must be made as soon as possible to permit a review by the Sponsor to determine the impact of the deviation on the patient and/or the study.

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

11.10 Financial Disclosure

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

11.11 Publication and Disclosure Policy

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

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

Corcept 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.

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APPENDICES

Appendix A: Schedule(s) of Activities

Table 11 Schedule of Clinical Assessments and Procedures

Study Procedure	Screening [a]	Baseline	Double-Blind, Placebo-Controlled Weeks 1 to 22						Early Termination	Follow-up [b]
Visit Name	—	—	**Week 2**	**Week 6**	**Week 10**	**Week 14**	**Week 18**	**Week 22**	**ET**	—
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Visit Window (d)	**−42 to −1**	—	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**-14/+7d**	**+14d**	**±7d**
Informed consent	X	-	-	-	-	-	-	-	-	-
Inclusion/exclusion criteria	X	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
Height, weight, waist circumference [e]	X	X	X	X	X	X	X	X	X	X
Vital signs [f]	X	X	X	X	X	X	X	X	X	X
Adverse events [g]	-	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X
12-Lead ECG (in duplicate)	X	-	-	-	-	X	-	X	X	-
Pregnancy test (women only) [h]	X (s)	X (u)	X (u)	X (u)	X (u)	X (u)	X (u)	X (u)	X (u)	X (u)
Chemistry [i], Hematology [j]	X	X	X	X	X	X	X	X	X	X

Study Procedure	**Screening [a]**	**Baseline**	**Double-Blind, Placebo-Controlled Weeks 1 to 22**						**Early Termination**	**Follow-up [b]**
Visit Name	**—**	**—**	**Week 2**	**Week 6**	**Week 10**	**Week 14**	**Week 18**	**Week 22**	**ET**	**—**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Visit Window (d)	**−42 to −1**	**—**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**-14/+7d**	**+14d**	**±7d**
Lipid-metabolism panel (fasting) [k]	-	X	-	-	-	-	-	X	X	-
Thyroid-function tests	X	-	-	-	-	-	-	-	-	-
Coagulation panel [l]	-	X	-	-	-	X	-	X	X	-
Serum osteocalcin	-	X	-	-	-	-	-	X	X	-
GR activity biomarker tests	X	-	-	X	X	X	-	X	X	-
2-hour oGTT [m]	X	X [n]	X	X	X	X	X	X	X	-
HbA1c [o]	X	X [n]	-	-	X	-	-	X	X	-
HPA-axis parameters [p]	X	-	-	X	X	X	-	X	X	-
24-hour UFC with creatinine [q]	X	-	-	-	-	-	-	-	-	-
DST with dexamethasone levels [r]	X	-	-	-	-	-	-	-	-	-
Late-night salivary cortisol [s]	X	-	-	X	X	X	-	X	X	-
Early-morning salivary cortisol [t]	X	X	-	X	X	X	X	X	X	-
ABPM (24-hour) test [u]	X	-	X	X	X	X	X	X [v]	X	-
DXA scan [w]	-	X [w]	-	-	-	-	-	X	X [w]	-
Pharmacokinetics, intensive	-	-	-	-	-	-	X	-	-	-

Study Procedure	Screening [a]	Baseline	Double-Blind, Placebo-Controlled Weeks 1 to 22						Early Termination	Follow-up [b]
Visit Name	—	—	**Week 2**	**Week 6**	**Week 10**	**Week 14**	**Week 18**	**Week 22**	**ET**	—
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Visit Window (d)	**−42 to −1**	—	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**-14/+7d**	**+14d**	**±7d**
Cushing QoL questionnaire	-	X	-	X	X	X	X	X	X	-
Beck Depression Inventory	-	X	-	X	X	X	X	X	X	-
Sit-to-stand test	-	X	-	X	X	X	X	X	X	-
Trail-making test	-	X	-	X	X	X	X	X	X	-
Dosing diary	-	X	X	X	X	X	X	-	-	-
Study-drug dispensing and/or adherence [x]	-	X	X	X	X	X	X	X [y]	X	-

ABPM, ambulatory blood pressure monitoring; BP, blood pressure; DST, dexamethasone suppression test; DXA, dual-energy X-ray absorptiometry, ECG, electrocardiogram; ET, early termination; GR, glucocorticoid receptor; HbA1c, hemoglobin A1c; HPA, hypothalamic-pituitary-adrenal; oGTT, oral glucose tolerance test; QoL, quality-of-life; (s), serum; (u), urine; UFC, urinary free cortisol.

a. All assessments done during Screening can be used as Baseline with the exception of oGTT, HbA1c, and 24-hour ABPM, which must be performed within 2 weeks of the Baseline Visit and used as Baseline. Medications used in the treatment of Cushing syndrome are prohibited and require washout of at least 12 weeks before Screening.
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.
c. For any medication used to treat hypercortisolism, hypertension, and/or diabetes 3 months prior to Day 1.
d. General physical appearance of patients during the examination will be assessed.
e. Height is measured at Screening only. Body weight and circumference will be measured at all visits.
f. Vital signs: BP, heart rate, respiratory rate, and body temperature.
g. Adverse events will be collected after the informed consent form is signed. Events ongoing at study entry are considered medical history.
h. Pregnancy tests: for women of childbearing potential: (s)=serum pregnancy test at Screening; (u)=urine pregnancy test at other time points.

i. Chemistry parameters: full chemistry profile that includes albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen, calcium, chloride, cholesterol, creatinine, fasting glucose, fasting insulin, lactate dehydrogenase, magnesium, phosphorus, potassium, sodium, creatine kinase, total and direct bilirubin, total protein, uric acid. Should be performed either before, or ≥24 hours after, the DST test.
j. Hematology parameters: a complete blood count and differential. Should be performed either before, or ≥24 hours after, the DST test.
k. Lipid-metabolism panel: total cholesterol, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, very low-density lipoprotein-cholesterol, and triglycerides. Should be performed either before, or ≥24 hours after, the DST test.
l. Coagulation panel: Factor VIII, von Willebrand factor, protein S, protein C, thrombin antithrombin (TAT), and partial thromboplastin time (PTT). Should be performed either before, or ≥24 hours after, the DST test.
m. oGTT, including measurement of glucagon levels at selected visits (i.e., Baseline Visit, Week 10, Week 22, and ET Visit [if applicable]; for patients with DM/IGT at Baseline): The 2-hour oGTT will be performed on all patients during Screening. During Screening, oGTT should be performed either before, or ≥24 hours after, the DST test. In patients with an increase to their DM medications before or during Screening, oGTT should be performed ≥4 weeks after the increase. The Screening 2-hour oGTT must be performed within 2 weeks of the Baseline Visit and used as Baseline. During treatment with study drug, a 2-hour oGTT will be performed only in patients with DM/IGT except at the Baseline Visit, Week 10, Week 22 and ET Visit (if applicable), when the 2-hour oGTT will be performed for all patients.
n. oGTT and HbA1c will only be performed at Baseline if the prior assessment was not performed within 2 weeks.
o. HbA1c: The HbA1c test will be performed on all patients during Screening. In patients who have an increase to their DM medications before or during Screening, HbA1c should be performed ≥4 weeks after the increase in the diabetes medication. The Screening HbA1c test must be performed within 2 weeks of the Baseline Visit and used as Baseline. During treatment with study drug, HbA1c will be performed only in patients with DM/IGT except at the Baseline Visit, Week 10, Week 22 and ET Visit (if applicable), when the HbA1c test will be performed for all patients.
p. HPA-axis: Early-morning plasma ACTH, fasting serum cortisol, and DHEA-S. HPA-axis tests should be performed either before, or ≥24 hours after, the DST test. ACTH should be measured at least twice during Screening.
q. 24-hour UFC test samples will be collected by the patient at home twice during Screening. The average of the results will serve as Baseline. UFC collection should be performed either before, or ≥24 hours after, the DST test.
r. DST: 1-mg overnight or 2-mg 48-hour dexamethasone test must be performed during Screening. Dexamethasone levels should be measured concurrently. Estrogen preparations, including birth control and hormone replacement treatments, should be withheld for a duration of at least 5 half-lives of the estrogen analogue prior to DST.
s. Two late-night salivary cortisol samples will be collected at Screening, one of which should be the night before the Day 1/Baseline Visit. During treatment with study drug, a late-night salivary-cortisol sample should be collected the night before the study visit. During Screening, salivary cortisol sample collection should be performed either before, or ≥24 hours after, the DST test.
t. Early-morning salivary cortisol will be collected at the site if the patient arrives before 9 am (to avoid mix up with the late-night salivary cortisol samples collected by the patient). If the visit is scheduled after 9 am, the sample will be collected at home by the patient the morning of the visit. Early-morning salivary cortisol should be collected either on the same day as the late-night salivary cortisol is collected, or the morning after.
u. ABPM: The 24-hour ABPM will be assessed for all patients during Screening. During Screening, in patients with an increase to their anti-hypertension medications either before or during Screening, ABPM should be performed ≥4 weeks after the increase in anti-hypertension medications. During Screening, ABPM should be performed either before, or ≥24 hours after, the DST test. ABPM must be performed within 2 weeks of the Baseline Visit and used as Baseline. During the study, ABPM measurements will be performed only for patients with systolic hypertension except at Week 10, Week 22, and ET Visit (if applicable), when ABPM will be performed for all patients.
v. Week 22 visit ABPM should be performed within 7 days prior to the visit.

w. DXA scan should be performed within 2 weeks of the Baseline Visit. Patients to get DXA scan before Baseline Visit only in the case they are already determined to qualify for the study. At ET visit (if applicable), DXA scan should not be repeated if it was already completed within 8 weeks prior to ET Visit; acceptable visit window is up to 3 months following ET Visit.
x. 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 the Week 18 visit, when it should be administered prior to blood draws for PK assessment.
y. Patients will remain on study drug post Week 22 until it has been confirmed that all results for efficacy assessments are available and no repeated assessments are required.

Appendix B: Summary of Changes

Significant changes in Amendment 3 of the protocol dated 11 October 2024 compared with Amendment 2 dated 21 June 2023 are summarized below with additional details in Table 12; deleted text is shown as a ~~strikethrough~~ and new text is shown in **bold**.

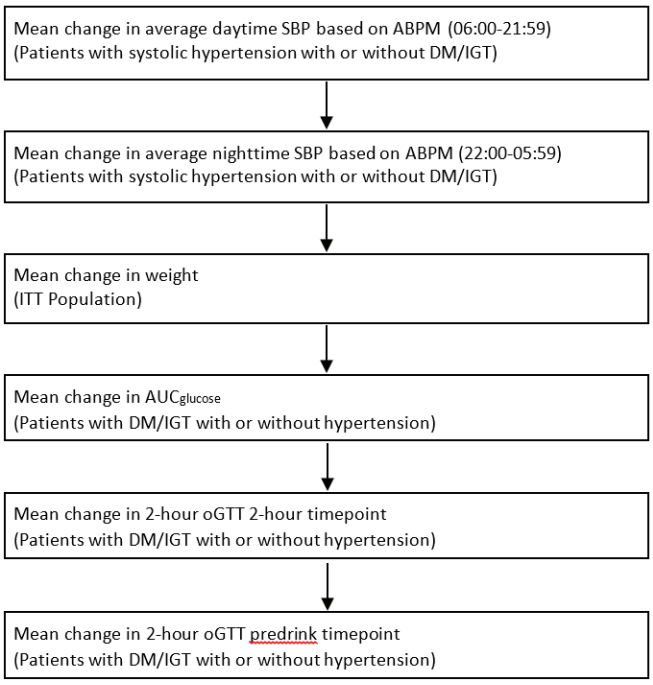
Minor editorial or stylistic changes made for consistency are not summarized and may not be shown in the redline version of the amendment (e.g., punctuation, spelling, abbreviations). Throughout the document, sections, tables, and figures were renumbered as appropriate. Table of Contents, lists of tables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

Significant revisions to the protocol include the following:

- Assessment of glycemic control was moved from a primary to secondary objective
- Primary and secondary endpoints are updated to align with the revision to study objectives
- Statistical analyses sections are updated to align with revisions to endpoints
- Imputation methods for missing data related to the primary analysis are updated to use a placebo wash-out multiple imputation method
- Endpoints for hyperglycemia are updated to include additional continuous endpoints
- Statistical analyses sections are updated to reflect gated testing approach of certain secondary endpoints

Table 12 Summary of Changes in Protocol CORT125134-456 Amendment 3

Section	Summary of Change	Revisions
Throughout the protocol	Updated version and date of the protocol.	Amendment ~~2~~ **3** ~~21 June 2023~~**11 October 2024**
Title page	Updated Sponsor address	Corcept Therapeutics Incorporated ~~149 Commonwealth Drive~~ ~~Menlo Park~~**101 Redwood Shores Parkway** **Redwood City,** California ~~94025~~**94065** USA (650) 327-3270
Synopsis	Updated text in synopsis revised to align with changes in the protocol body.	--
Throughout the protocol	Updated text throughout to present hypertension before DM/IGT for consistency with revisions to endpoints	--
2.1 Primary Objectives	Updated to remove glycemic control as a primary objective	To assess the efficacy of relacorilant for the treatment of hypercortisolism in patients with cortisol-secreting adrenal adenomas or hyperplasia, based on ~~glycemic and~~ blood pressure (BP) control at Week 22 compared with placebo
2.2 Secondary Objectives	Updated to include glycemic control as a secondary objective	To assess changes in cortisol excess-related comorbidities (e.g., body weight **and glycemic control**) in patients with hypercortisolism due to cortisol-secreting adrenal adenomas/hyperplasia
3.2.1 Primary Endpoints	Updated to remove measure of $AUC_{glucose}$ (glycemic control) as a primary endpoint	~~In patients with DM/IGT, the mean change in AUCglucose, from Baseline to Week 22 as compared between relacorilant and placebo arms.~~
3.2.2 Secondary Endpoints	Updated to include $AUC_{glucose}$ as a secondary endpoint for hyperglycemia	**1. In patients with DM/IGT at Baseline, the mean change in $AUC_{glucose}$, from Baseline to Week 22 as compared between relacorilant and placebo arms.**
	Added additional continuous endpoints for hyperglycemia	**9. In patients with DM/IGT in the ITT population, the proportion of patients who achieved decrease of $AUC_{glucose}$ of ≥25%, ≥10%, ≥5% and any decrease from Baseline to Week 22.** **10. In patients with DM/IGT in the ITT population, the mean change in 2-hour oGTT 2-hour timepoint from Baseline to Week 22.** **~~7.~~11. In patients with DM/IGT in the ITT population, the mean change in 2-hour oGTT predrink timepoint from Baseline to Week 22.**
9.1 Analysis Populations	Updated Table 10 to remove $AUC_{glucose}$ named as a primary endpoint	The mITT population will include all patients in the ITT population with ≥1 post-randomization efficacy assessment the primary **and secondary** efficacy endpoints **of ABPM and/or** $AUC_{glucose}$~~or ABPM).~~**.** This population will be used for sensitivity analyses performed on the primary and secondary efficacy endpoints. **The mITT population can vary for different efficacy endpoints.**

Section	Summary of Change	Revisions
9.2 General Statistical Considerations	Revised timing for finalization of the statistical analysis plan	Statistical methods will be prespecified and documented in detail in a statistical analysis plan, to be finalized before ~~database lock~~**study unblinding**.
9.3 Hypothesis Testing	Updated section to describe gated testing approach for certain secondary endpoints	For the testing of the primary **and certain secondary** efficacy endpoints, adjustment for multiplicity will be implemented to maintain a 2-sided 0.05 significance level for the Family-Wise type I error rate. **In order to provide strong control of the Type I error, certain secondary analyses will be tested using a gated testing approach at a 2-sided alpha level of 0.05. If the null hypothesis is rejected for the primary endpoint, certain secondary endpoints will be sequentially tested following the gatekeeping hierarchy (Figure 2). No adjustments for multiplicity will be made for other secondary or exploratory endpoints.** **Figure 2: Sequential Gatekeeping Hierarchy**  ~~Primary efficacy endpoints are defined in Section 3.2.13.2.1. The study will be considered to have a positive outcome if either of the 2 primary endpoints reaches statistical significance.~~ ~~To adjust for multiplicity for the 2 primary efficacy endpoints, a Hochberg step-up procedure (Hochberg 1988; FDA 2017) will be conducted as follows:~~ ~~1. At the first step of the procedure, the larger 2-sided p-value of the 2 primary endpoints will be compared with the 0.05 significance level.~~ ~~2. If the larger p-value is <0.05, responses with respect to both glycemic control and hypertension will be declared statistically significant.~~

Section	Summary of Change	Revisions
		~~3. If the larger p-value is >0.05, the other primary endpoint will be declared statistically significant if the corresponding 2-sided p-value is <0.025.~~ ~~4. Otherwise, neither of the 2 primary endpoint results will be considered statistically significant.~~ All statistical hypotheses for **any other** secondary **endpoints** and exploratory endpoints will be tested at a 2-sided 0.05 significance level unless otherwise specified.
9.5.4.1 Analysis of Primary Efficacy Endpoint	Removed analysis of glycemic control (AUCglucose) from primary analysis and revised imputation methods for missing data related	~~For the DM/IGT subgroup, the estimand of interest is the between-treatment difference in change in AUCglucose from Randomization to Week 22 (estimated using a mixed model for repeated measures [MMRM] model). All available values for AUCglucose will be used for analysis in the MMRM model, regardless of treatment adherence.~~ ~~If there are a sufficient number of retrieved dropouts (at least 10 patients who discontinue treatment but still had an AUCglucose assessment at Week 22), imputation of missing data at Week 22 (for non-retrieved dropouts) will be performed based on known measurements from the retrieved dropouts with similar baseline characteristics for patients discontinuing the study without use of rescue medication, but placebo-mean imputation at visits after initiation of rescue medication for patients that use rescue medication.~~ ~~For patients who use rescue medication for hyperglycemia control before Week 22, the plasma 2-hours oGTT test values collected after first use of rescue medication will not be included in the primary analysis. Rather, patients who use rescue medication for hyperglycemia control are assumed to perform similarly to patients who received placebo. And, therefore, the missing AUCglucose values after initiation of rescue medication in patients treated with relacorilant that receive diabetes rescue medication are replaced with the estimated mean of the entire endpoint distribution of the placebo arm at visits after initiation of rescue medication (this is the placebo-based mean value at each visit).~~ ~~The primary efficacy analysis for the primary endpoint of change in AUCglucose from Randomization to Week 22 will be performed using a linear mixed model for repeated measures (MMRM) using data with the imputation method described above. Restricted maximum likelihood (REML) estimation will be used. The MMRM model will include Baseline AUCglucose as a covariate; treatment, visit, and treatment by visit interaction, and stratification factor as fixed effects; patients within treatment groups as random effects. In the DM/IGT subgroup, the stratification factor at randomization identifies patients with or without hypertension. 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.~~ ~~The primary analysis will determine whether there is a difference between treatment groups in terms of change in~~

Section	Summary of Change	Revisions
		~~AUCglucose from Randomization to Week 22. This will be accomplished by using appropriate linear contrasts of the parameters in the MMRM model described above.~~ ~~Multiple imputation will be implemented to allow additional source of variability in the imputed values. For each imputed dataset, the same MMRM model specified above will be used to estimate treatment effect on change in AUCglucose from Randomization to Week 22. The combination of individual estimates for treatment effect and the inference based on the combined estimate will be handled by SAS procedure MIANALYZE. Additional sensitivity analyses will be specified in the statistical analysis plan (SAP).~~ For the hypertension subgroup **of the ITT Population**, the estimand of interest is the between-treatment difference in change in average SBP based on 24-hour ABPM from Randomization to Week 22 (estimated using a MMRM model). All available values for SBP will be used for analysis in the MMRM model, regardless of treatment adherence. ~~If there are a sufficient number of retrieved dropouts (at least 10 patients who discontinue treatment but still had an SBP assessment at Week 22), imputation of missing data at Week 22 (for non-retrieved dropouts) will be performed based on known measurements from the retrieved dropouts with similar baseline characteristics for patients discontinuing the study without use of rescue medication, but placebo-mean imputation at visits after initiation of rescue medication for patients that use rescue medication.~~ **For patients who use rescue medication or discontinue treatment early, a placebo wash-out multiple imputation will be used as the primary analysis. For those patients who use rescue medication for hypertension after randomization and before Visit Week 22, the values collected after first use of rescue medication are irrelevant to the clinical question of interest and will not be used in the analysis. For patients who discontinue treatment early, all collected values (including retrieved drop-outs) will be used in the analysis.**~~For patients who use rescue medication for hypertension control before Week 22, the average SBP based on 24-hour ABPM collected after first use of rescue medication will not be included in the primary analysis. Rather, patients who use rescue medication for hypertension control are assumed to perform similarly to patients who received placebo. And, therefore, the missing average SBP after initiation of rescue medication in patients treated with relacorilant that receive hypertension rescue medication are replaced with the estimated mean of the entire endpoint distribution of the placebo arm at visits after initiation of rescue medication (this is the placebo-based mean value at each visit).~~**The 'placebo wash-out' analysis means the missing 24-hour average SBP at Visit Week 22 data will be imputed by considering a wash-out of the effect of treatment using completers in the placebo arm.**

Section	Summary of Change	Revisions
		Specifically, 24-hour average SBP data for patients on the placebo arm without measurements at Week 22 will be imputed using a monotone regression model based on observed 24-hour average SBP data of completers on the placebo arm with intermediate measurements, Baseline value and stratification factor. For patients on the relacorilant arm with missing Week 22 data, the imputation model with only Baseline value and stratification factor will be used. … Additional sensitivity analyses **of the primary endpoint, including subgroups of interest**, will be specified in the SAP. ~~Additional sensitivity analyses of the primary endpoints by subgroups of interest will be done. Details will be described in the SAP.~~
9.5.7 PD Analysis	Revised timing for finalization of the statistical analysis plan	Analysis of PD endpoints will be described in a separate PD analysis plan finalized before~~ database lock~~**study unblinding**.
9.5.8 Biomarker/ Pharmacogenetic Analysis	Revised timing for finalization of the statistical analysis plan	Biomarker and pharmacogenetic exploratory analyses will be described in the SAP finalized before~~ database lock~~**study unblinding**.