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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DOCUMENTATION OF STATISTICAL METHODS

Document Title and Version	Date
Statistical Analysis Plan, Version 2.0	11 October 2024

STATISTICAL ANALYSIS PLAN
STUDY 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**
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APPROVAL SHEET

STATISTICAL ANALYSIS PLAN

CORT125134-456: 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

Reviewed and Accepted at Corcept Therapeutics Incorporated by

[redacted]

CONTENTS

List of Tables

List of Figures

LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
ABPM	ambulatory blood pressure monitoring
ACTH	Adrenocorticotropic Hormone
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomic Therapeutic Chemical
AUC	area under the concentration-time curve
$AUC_{glucose}$	area under the concentration-time curve for glucose
BDI-II	Beck Depression Inventory®-II
BMI	Body Mass Index
BP	Blood Pressure
CMH	Cochran-Mantel-Haenszel
CI	confidence interval
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV (%)	coefficient of variation (%)
DBP	diastolic blood pressure
DM	diabetes mellitus
DXA	dual energy X-ray absorptiometry
ECG	Electrocardiogram
eCRF	electronic case report form
ET	early termination
FDA	Food and Drug Administration
FKBP5	FK506 binding protein 5
GR	glucocorticoid receptor

Abbreviation	Definition
HbA1c	hemoglobin A1c
HPA	hypothalamic-pituitary-adrenal
ICF	informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH)
IDMC	Independent Data Monitoring Committee
IGT	impaired glucose tolerance
IRT	Interactive Response System
ITT	Intent-to-treat population
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed model for repeated measures
mRNA	messenger RNA
oGTT	oral glucose-tolerance test
OL	open label
PD	Pharmacodynamic
PK	Pharmacokinetics
PP	Per Protocol Analysis Population
QoL	quality-of-life
REML	restricted maximum likelihood
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	Standard Deviation
SE	Standard Error
SI	Système International

Abbreviation	Definition
TEAE	treatment-emergent adverse event
UFC	urinary free cortisol
US	United States
vs.	Versus
WHO	World Health Organization

1 INTRODUCTION

The purpose of the statistical analysis plan (SAP) is to provide a detailed description of the principal features of the analysis described in the protocol and to include detailed procedures for executing the statistical analysis of the primary and secondary endpoints and other data for Corcept Study CORT125134-456.

This SAP contains definitions of analysis populations and endpoints, outlines the timing of statistical analyses, and provides a comprehensive description of statistical analyses to be implemented to assess the clinical efficacy and safety of treatment with relacorilant as per Protocol CORT125134-456: 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. The statistical methods applied in the design and planned analyses of this study are consistent with the International Conference on Harmonization of Technical Requirements for Pharmaceuticals for Human Use, Guidance for Industry: *E9 Statistical Principles for Clinical Trials* (ICH E9 1998) and *E9 (R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials* (ICH E9[R1] 2021).

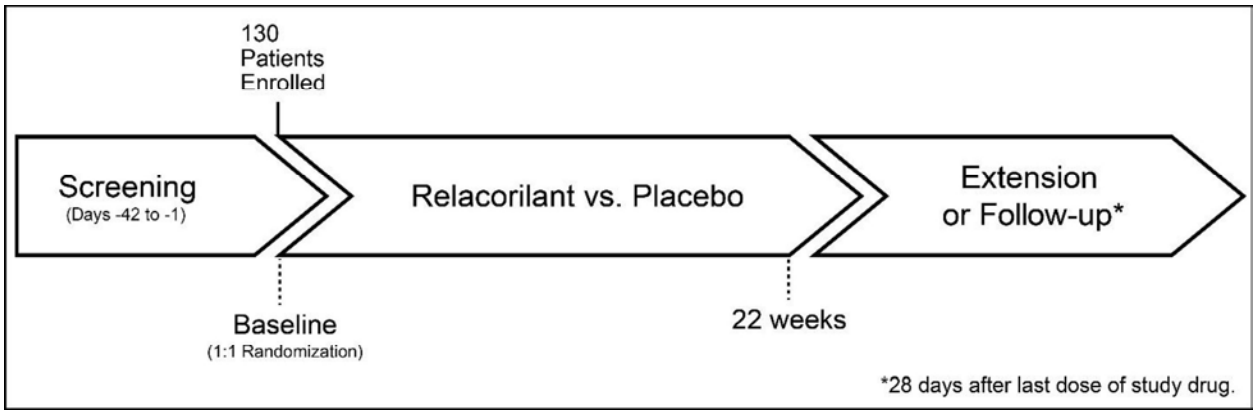
This SAP will be finalized before study unblinding and prior to data analysis to provide full details of statistical analysis to be presented in the clinical study report (CSR). Any changes between the statistical methods provided in the clinical study protocol and this SAP will be explained herein; the methods described in the SAP take precedence over the protocol; any changes or deviations from this SAP relative to the final analysis will be fully documented in the CSR. Minor changes or deviations from the templates for tables, figures, and listings need not be documented in the CSR.

2 STUDY OVERVIEW

2.1 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).

Figure 1 CORT125134-456 Study Design



3 STUDY OBJECTIVES

3.1 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.

3.2 Secondary Objective

- 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.

3.3 Exploratory Objective

- 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.

4 STUDY ENDPOINTS

4.1 Primary Efficacy Endpoint

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

4.2 Safety Endpoints

In all patients, assessment of safety is based on TEAEs.

4.3 Secondary Endpoints

Secondary endpoints will include data from Baseline to Week 22 to compare the treatment difference between relacorilant and placebo.

Endpoints for Hypertension:

1. In patients with systolic hypertension at Baseline, the mean change in 24-hour average diastolic blood pressure (DBP), and heart rate (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 ABPM).
3. In patients with systolic hypertension at Baseline, mean change in nighttime average SBP, DBP, and HR (based on 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, 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.

4.4 Exploratory 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); DHEA-S concentrations; ACTH concentrations; lipids (total cholesterol, LDL cholesterol, triglycerides, and very-low-density lipoprotein cholesterol [VLDL]); HPA-axis; 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 and psychosocial and physical problem subscales.

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. The analysis of pharmacokinetic data will be included in a separate pharmacokinetic SAP.

The analysis of biomarkers related to GR activity (such as FKBP5) will be included in a separate biomarker SAP.

5 SAMPLE SIZE CONSIDERATION

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 hypertension (39 per treatment group) will ensure at least 90% power to detect a difference between placebo and treatment arms of 7 mmHg in mean change from Baseline of the average SBP (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 is assumed in this calculation.

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 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.

Given the adjustment to a single primary endpoint of change from Baseline in the 24-hour average SBP (based on ABPM), Table 1 describes the power to detect a difference of 7 mmHg in mean change from Baseline of the average SBP with varying common standard deviations and a 0.05 two-sided significance level two-sided t-test.

Table 1 Statistical Power for Single Primary Analysis of Change from Baseline in 24-hour Average Systolic Blood Pressure

Common Standard Deviation	Power
7.5 mmHg	98.25%
8.0 mmHg	96.82%
8.5 mmHg	94.85%
9.0 mmHg	92.38%
9.5 mmHg	89.48%
10.0 mmHg	86.26%

Note: Given a sample size of 78 patients (39 patients per treatment group), an assumed difference of 7 mmHg in mean change from Baseline of the average SBP and the specified common standard deviation, the power to detect the difference is provided using a two group t-test with a 0.05 two-sided significance level.

6 ANALYSIS POPULATION

6.1 Enrolled Population

All patients who sign the informed consent form (ICF).

6.2 Safety Population

All patients who receive relacorilant or placebo and who take ≥ 1 dose of study treatment. Patients will be analyzed according to the treatment they actually received.

6.3 Intent to Treat Population (ITT)

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.

6.4 Modified Intent to Treat Population (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 $AUC_{glucose}$. Specifically, for patients in the systolic hypertension only or systolic hypertension and DM/IGT subgroup, at least 1 post-randomization ABPM assessment is required. For patients in the DM/IGT only subgroup, at least 1 post-randomization $AUC_{glucose}$ is required. This population will be used for sensitivity analyses performed on the primary and secondary efficacy endpoints.

6.5 Per-Protocol Population (PP)

The PP population will include all patients in the mITT population who had no important protocol deviations that might impact the validity of the primary efficacy analysis. Patients in the PP population who complete the study without an important deviation will be used in sensitivity analyses of the primary efficacy endpoint.

6.6 Key Subgroups

Cushing Syndrome Comorbidity Type at Baseline based on CRF collected data:

- Patients with systolic hypertension (average SBP ≥ 130 to ≤ 170 mm Hg) with or without DM/IGT
- Patients with DM/IGT with or without systolic hypertension
- Patients with DM/IGT only
- Patients with systolic hypertension only
- Patients with both DM/IGT and systolic hypertension
- Patients with DM (fasting plasma glucose ≥ 126 mg/dL or /or 2-hour oGTT plasma glucose ≥ 200 mg/dL at 2 hours or HbA1c ≥ 6.5%)
- Patient with impaired glucose tolerance (plasma glucose <126 mg/dL and < 200 mg/dL on a 2-hour oGTT at 2 hours and HbA1c < 6.5%)

6.7 Additional Subgroups

Patients with hypertension at Baseline:

- Patients on vs. off diuretic treatment based on prior medication.
- Patients treated with more than 3 prior antihypertensive medications, including a diuretic based on prior medication vs. less than or equal to 3 prior antihypertensive medications.
- Patients with DST with serum cortisol concentrations between 1.8 and 5 ug/dl vs. > 5 ug/dl at screening/Baseline.

Patients with DM/IGT at Baseline:

- Treated with prior antidiabetic medications.
- Not treated with prior antidiabetic medications.

Other subgroups of interest:

- Patient without prior long-acting insulin.
- Biological sex assigned at birth.
- Age: < 45 vs. 45–< 65 vs. ≥ 65.
- Race: White, African American, Other.
- Ethnicity: Hispanic vs Non-Hispanic
- Menopausal status: post-menopausal vs. pre-menopausal
- Geographic location: North America vs Rest of the world.
- BMI (kg/m^2) (< 25, 25–29, 30–< 35, and ≥ 35)

7 DEFINITIONS, COMPUTATIONS, AND CONVENTIONS

The statistical principles applied in the design and planned analyses of this study are consistent with Guidance for Industry FDA (US Food and Drug Administration) Guidance: *E9 Statistical Principles for Clinical Trials* (ICH E9 1998) and *E9 (R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials* (ICH E9[R1] 2021).

All statistical analyses detailed in this SAP will be conducted using SAS version 9.4 or higher.

All SAS programs that create tables, listings or figures and supporting analysis datasets will be validated per standard operating procedures.

7.1 Definitions

Study day: Calculated in reference to the date of first dose of relacorilant or placebo (Study Day 1). For assessments conducted on or after the first dose date, study day is calculated as (assessment date – first dose date + 1). For assessments conducted before the first dose date, study day is calculated as (assessment date – first dose date). There is no Study Day 0.

Treatment-emergent period: Is defined as the period of time from the date of the first dose of study drug through 28 days after the last dose of study drug. The treatment-emergent period will be used in the summaries of treatment-emergent adverse events (TEAEs).

7.1.1 Definitions of Baseline

The Baseline for oGTT plasma glucose will be defined for purposes of analyzing $AUC_{glucose}$. Baseline oGTT plasma glucose is defined as the last non-missing oGTT measurement prior to first dose of study drug. Non-missing oGTT measurement will be defined as a measurement with sufficient data for derivation of $AUC_{glucose}$ (Section 7.6.1). Therefore, the Baseline for $AUC_{glucose}$ is defined at the same visit (unscheduled or scheduled) that the Baseline oGTT plasma glucose is defined.

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

The Baseline for twelve-lead ECG interval parameters is defined as the average of the duplicate readings at Screening.

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

7.1.2 Definition of Analysis Visit Windows

In analysis of data summarized by study visit, unscheduled and early termination visits will be reassigned an analysis visit where data is scheduled for collection based on the planned visit Study Day.

The window for each study visit is relative to the Baseline visit. The protocol specified 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). The analysis visit windows are defined to cover all study days for a participant in the trial.

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.

The randomization day is considered Study Day 1.

Table 2 outlines the analysis visit windows.

Table 2 Analysis Visit Windows for Assessments

Visit Name	Start Day	Target Day	End Day
Baseline		1	
Week 2	2	15	29
Week 6	30	43	57
Week 10	58	71	85
Week 14	86	99	113
Week 18	114	126	140
Week 22	141	155	176
Follow-up	Study day of last dose of study drug +21	Study day of last dose of study drug +28	Study day of last dose of study drug +35

7.2 Reporting Conventions

Unless otherwise specified, the following conventions will be applied to all analyses:

- Continuous variables will be summarized to indicate the population sample size (N), number of patients with available data (n), mean, standard deviation (SD), median, inter-quartile range (Q1, Q3), minimum, maximum and 95% confidence intervals (CI).
- Categorical variables will be summarized by the population size (N), number of patients with available data (n), number of patients in each category, percentage of patients in each category and 95% CI. Unless otherwise noted, the denominator to determine the percentage of patients in each category will be based on the number of patients with available data (n).
- Select ordinal data may be summarized using both descriptive statistics and counts and percentages of patients in each category, as appropriate.
- Confidence intervals (CIs), when presented, will generally be constructed at the 95% level. For binomial variables, exact methods will be employed unless otherwise specified.

- Rounding conventions for presentation of summary statistics will be based on the precision of the variable of summarization, as it is collected in its rawest form (i.e., on the eCRF or as provided within an external file) and are outlined as follows:
    - The mean and median will be rounded to one more decimal place than the precision of the variable of summarization.
    - Measures of variability (e.g., SD, SE) will be rounded to two more decimal places than the precision of the variable of summarization; and
    - Minimum and maximum values will be presented using the same precision as the variable of summarization.
    - Non-zero percentages will be rounded to 1 decimal place. Number and percentage values will be presented as xx (xx.x%).
- Analysis and summary tables will have the analysis population sample size (i.e., number of patients).
- The descriptive summary for observed end of treatment visit will be included in all by visit summary table.
- Laboratory data will be reported using standard international (SI) units and conventional unit; as central laboratories are used for this study, conversion factors from conventional units to SI units will be listed in the clinical study report.
- 1 inch = 2.54 cm.
- For by-visit observed data analyses, percentages will be calculated based on the number of patients with non-missing data as the denominator unless otherwise specified.
- P-values will be rounded to 4 decimal places. P-values that round to 0.0000 will be presented as '< 0.0001' and p-values that round to 1.000 will be presented as '> 0.9999'.
- Medical history and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 26.0 or later). Adverse event severity will be evaluated using the National Cancer Institute *Common Terminology Criteria for Adverse Events* (CTCAE) v.5.0 (NCI-CTCAE 2017).
- Prior therapies and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (version WHO Drug Global B3 March, 2023) and summarized by Anatomical Therapeutic Chemical (ATC) medication class and preferred names.
- All statistical hypotheses will be tested at a two-sided 0.05 significance level unless otherwise specified.
- Listings will be presented in the order of patient identifier, comorbidity type (DM/IGT or Hypertension), and visit (or date of procedure or event, when applicable), unless stated otherwise.

7.3 Summarization by Visit

Data collected at scheduled visits will be analyzed based on the nominal visit as reported in the database. If an unscheduled assessment is mapped to an analysis visit window that already has a non--missing assessment for the corresponding scheduled visit, the scheduled visit will be used in the analysis. Otherwise, if multiple assessments occur within a single visit window, then the closest assessment to the target day of the visit window will be used in the analysis. If distance to target visit date is the same for more than one assessment (e.g., one assessment is performed 2 days prior to the target visit date and one assessment is performed 2 days after the target visit date), the later assessment day that is still within the visit window will be used in the analysis.

If there are repeated assessments of the same sample or procedure at a scheduled visit, the most recent value will be used for analysis.

7.4 Data Handling Rules

Unless otherwise noted, values reported as greater than or less than limit of quantification (LOQ) (e.g., "< 1.0") will be summarized with the sign suppressed in summary tables and figures, using the LOQ value instead.

7.5 Standard Calculations

Conventions for calculations with dates are as follows:

- Dates will be stored as numeric variables in the SAS analysis files and reported in DDMMMYYYY format (i.e., the Date9. datetime format in SAS).
- Dates recorded in comment fields will not be imputed or reported in any specific format.
- Age will be calculated in years as integer part of (DATE of ENROLLMENT - DATE of BIRTH + 1)/365.25. If both day and month fields are missing, impute missing day and month as July 1st. If the year field is missing, age will be set as missing.
- Where appropriate, the calculated study day of each assessment or event will be presented with the assessment or event date on patient data listings, where study day is defined in Section 7.1.
- Days: A duration between two dates expressed in days will be calculated using the following conventions:
    - (Later date – earlier date) + 1, if the earlier date is on or after the date of first dose of study drug; or
    - Later date – earlier date, if the earlier date is prior to the date of first dose of study drug.
- Weeks: A duration expressed in Weeks will be calculated by dividing the duration in days by 7.
- Months: A duration expressed in months will be calculated by dividing the duration in days by (30.4375=365.25 / 12).

- Years: A duration expressed in years will be calculated by dividing the duration in days by 365.25.

Detailed rules for imputation of missing/partially missing dates for adverse events and prior/concomitant medications/procedures are provided in Section 7.6.4.

Conventions for calculations for other types of variables:

- Change from Baseline: Change from Baseline will be calculated as the post-Baseline value minus the Baseline value.
- Percentage Change from Baseline: Percentage change from Baseline will be calculated as the change from Baseline divided by the Baseline value, multiplied by 100.

7.6 Handling Missing Data

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

All efforts will be made to prevent missing data. To prevent bias caused by unavoidable missing data, different statistical approaches (described in Section 7.6.1 through Section 7.6.5) based on the nature of the endpoint will be used to handle missing data. For each endpoint, a summary of missing data at each of the visits will be presented by treatment arm and by visit.

7.6.1 Handling Missing Data for Primary Efficacy Endpoint

As described in the protocol, if a patient discontinues early from the study, the patient is instructed to return for Visit Week 22 per the patient's original dosing schedule. Retrieved dropouts are patients who discontinue study treatment prior to Visit Week 22 and return for the Visit Week 22 assessment as required by protocol. Missing data for patients who use rescue medication or discontinue treatment early will be imputed using a placebo wash-out multiple imputation. For patients who discontinue treatment early, all collected values (including retrieved drop-outs) will be used in the analysis. Further details are given in Section 9.8.1.3.

7.6.2 Handling Missing Data for Secondary Efficacy Endpoints

7.6.2.1 Endpoints Summarized with Proportions

For endpoints that are defined as response to certain criteria, patients with missing data at Visit Week 22 will be considered non-responders.

7.6.2.2 Continuous Secondary Efficacy Endpoints

For calculations involving AUC based on plasma 2-hours oGTT test, the following rules for handling missing data will be applied:

- If the pre-glucose drink time point or 30-minute post-glucose drink time point are missing, no AUC calculation will be performed. The AUC for that visit will be counted as missing.

- If more than one post-glucose drink time points are missing, no AUC calculation will be performed.
- If only one post-glucose drink time point is missing, and it is not the 30-minute post-glucose drink time point, then the AUC will be calculated using available data. For example, if the 90-minute time point is missing, a trapezoid will be constructed to connect the 60 minute and 120-minute time points.
- If only the 120-minute post-glucose drink time point is missing, the AUC will be calculated using the available data and AUC, and that AUC pre-glucose drink to 90minute post-glucose drink value will be used in the summary tables.
- Otherwise, observed values only will be used.

All other efficacy by-visit analyses will include summaries for the observed cases only, where no imputations will be used, except for the primary endpoint, 24-hour average SBP for which missing data handling rules are described above.

7.6.3 Handling Missing Data for Exploratory Efficacy Endpoints

For calculations involving exploratory efficacy endpoints, the same rules for handling missing data as described above for Secondary Efficacy Endpoints will be applied (i.e. observed cases only will be used in by-visit analyses and no imputations will be applied).

7.6.4 Handling Incomplete or Missing Dates for Adverse Events and Concomitant Medications

For safety analyses, incomplete date of last dose of study drug and incomplete start date of concomitant medications that are missing the day of the month, the 15th of the month will be used to impute the missing date. When imputing partial last dose dates, the last visit date will be taken into consideration. The imputed dates will be used to determine the treatment-emergent period.

For adverse events with a partial date, available date parts (year, month, and day) of the partial date will be compared with the corresponding date components of the start date and end date of the treatment-emergent period to determine if the event is treatment emergent. The following rules will be applied to impute partial dates for adverse events.

If start date of an adverse event is partially missing, following imputation rules will be applied:

- If both Month and Day are missing and Year = Year of treatment start date, then set to treatment start date.
- If both Month and Day are missing and Year ≠ Year of treatment start date, then set to January 1.
- If Day is missing and Month and Year = Month and Year of treatment start date, then set to treatment start date.
- If Day is missing and Month and Year ≠ Month and Year of treatment start date, then set to first of the month.

- If start date is completely missing, set to treatment start date as long as adverse event end date is not prior to treatment start date.

If end date of an adverse event is partially missing, following imputation rules will be applied:

- If both Month and Day are missing, then set to December 31.
- If only Day is missing, then set to last day of the month.
- If end date is completely missing, do not impute.

When the start date or end date of a medication is partially missing, the date will be imputed to determine whether the medication is prior or concomitant (or both). The following rules will be applied to impute partial dates for medications:

If start date of a medication is partially missing, following imputation rules will be applied:

- If both Month and Day are missing, then set to January 1.
- If only Day is missing, then set to the first day of the month.

If end date of a medication is partially missing, following imputation rules will be applied:

- If both Month and Day are missing, then set to December 31.
- If only Day is missing, then set to last day of the month.

If start date or end date of a medication is completely missing, no imputation is applied.

7.6.5 Handling Incomplete or Missing Dates for Medical History

If the diagnosis date of Cushing disease is incomplete, month will be imputed as the first month of the year, and day will be imputed as the first day of the month. Missing year will not be imputed. Same rules for handling missing diagnosis date of Cushing disease will be applied to other medical disease that patients have been diagnosed.

8 TIMING OF ANALYSES

8.1 Interim Analysis

No interim analyses are planned for purposes of early stopping of the study or modifying the study design. However, data may be reviewed periodically by the Sponsor, as needed.

8.2 Final Analyses and Reporting

All planned analyses described in the SAP will be performed after the last patient has completed the study, all outstanding queries resolved, and the database has been locked and unblinded. The SAP must be signed off prior to study unblinding.

9 STATISTICAL METHODS

9.1 General Statistical Consideration

Statistical analyses will be reported with tables, figures, and listings, presented in rich text format, and using recommended ICH numbering. Output specifications for all tables, figures, and listings will be in conformance with guidelines specified by the ICH of the Electronic Common Technical Document Specification (ICH M2 eCTD 2003).

9.2 Patient Disposition

Patient disposition will be summarized for the ITT population. Participant disposition will present the number of patients randomized, number treated with study drug, and among those number of patients who completed the study, discontinued from the study, number who discontinued from study treatment, reasons for study discontinuation and reasons for study drug discontinuation. Primary reason for discontinuation of treatment, including any of the following, will be summarized by treatment group:

- Adverse Event
- Lost to Follow-up
- Pregnancy
- Study Terminated by Sponsor
- Withdrawal by Patient
- Physician Decision
- Death
- Non-Compliance with study drug
- Protocol Deviation
- Other

A listing of all patients who discontinued the study and their reason for discontinuation will be provided.

If applicable, eligibility violations and occurrences of emergency and accidental treatment unblinding will be reported.

Attendance at scheduled visits will be shown as the number of patients who completed each scheduled visit.

9.3 Protocol Deviations

All important protocol deviations will be determined and appropriately categorized prior to database lock according to protocol deviation specification document. Protocol deviations will be listed study site, patient, and date of deviation, and will indicate if they are considered important. The number and percentage of patients with any important protocol deviations as well as the

number and percentage of patients with deviations by comorbidity type (DM/IGT or Hypertension), and overall, will be presented for the Safety Population.

9.4 Demographic Characteristics and Baseline Characteristics

The following demographic characteristics will be presented in listings and summarized for the ITT and Safety Analysis Population, (by treatment arm and overall):

- Age
- Sex
- Fertility status
- Ethnicity
- Race
- Geographic region: North America and Rest of the World (Austria, Bulgaria, Germany, Israel, Italy, Poland, Romania, and Spain)

Age will be summarized using descriptive statistics. Sex, ethnicity, race, fertility status, and geographic region will be summarized by the number and percentage of patients in each parameter category.

Baseline characteristics including height, weight, body mass index (BMI), waist circumference, plasma ACTH, 24-hr UFC, late-night salivary cortisol, DHEA-S levels, oGTT plasma glucose, $AUC_{glucose}$, HbA1c, osteocalcin, and 24-hour average systolic and diastolic BP from ambulatory BP monitoring (ABPM) will be summarized separately. BMI is calculated as: weight (kg) / [height (cm) / 100]^2.

Demographics and Baseline characteristics will be summarized by comorbidity subgroups in the ITT population.

9.5 Medical History

Medical history will be presented in listings and summarized for all patients in the ITT population and presented by comorbidity type, and overall. Frequency counts and percentages will be presented to summarize patients reporting medical history by system organ class and preferred term (coded using MedDRA version 26.0 or higher). History of hypercortisolism will be presented separately including type of imaging, imaging results, benign vs. malignant, adrenal lesion history, and DST history.

9.6 Prior and Concomitant Medications

Medications will be coded using the World Health Organization (WHODrug Global B3 March, 2023) dictionary. Medications entered on the eCRF will be mapped to ATC drug class (level 4) and drug name. Prior and concomitant medications will be summarized for the Safety Population.

Prior and concomitant medications will be summarized separately. Whether or not the medication is prior and/or concomitant will be determined programmatically based on medication start and end dates. A prior medication is defined as any medication administered that started prior to the date of the first dose of study drug. A concomitant medication is defined as any medication administered on or after the date of the first dose of study drug. A medication may be defined as both prior and concomitant. Imputation of partial dates apply as described in Section 7.6.4.

For the prior medications table summary, the number and percentage of patients receiving any medication will be summarized by comorbidity type, and all patients combined, as will the number and percentage receiving any medication by ATC drug class and generic drug name. For all concomitant medications table summaries, the number and percentage of patients receiving any medication will be summarized by treatment, comorbidity type, and all patients combined, as will the number and percentage receiving any medication by ATC drug class and generic drug name. Patients reporting use of more than one medication at each level of summarization (any medication received, ATC class, and generic drug name) will be counted only once. ATC class terms will be displayed alphabetically and by descending order of incidence for generic drug names within each ATC class. Whether or not the medication is prior and/or concomitant will be presented on the listing of prior and concomitant medications.

Concomitant medications will also be summarized by the following:

- Medications used in greater than or equal to 20% of the patients in the Safety Population; and
- Medications used to treat diabetes or hypertension for patients in the Safety Population.

The medication indication, e.g. antidiabetic, antihypertensive, and antidepressant, will be identified by the clinical team. Tables summarizing reduction in antidiabetic and antihypertensive concomitant medications will also be presented by comorbidity type (DM/IGT or Hypertension), and will include the number of patients taking the medication at Baseline, number of patients with a dose reduction, the number of patients with any reduction in daily dose, the number of patients with any increase in daily dose, the number of patients with $< 25\%$ reduction in daily dose, the number of patients with $\geq 25\%$ and $\leq 50\%$ reduction in daily dose, the number of patients with $\geq 50\%$ reduction in daily dose, and the number of patients with complete discontinuation in daily dose. Antidiabetic and antihypertensive medications will be those that are entered as antidiabetic or antihypertensive on the eCRF, potassium sparing diuretics for antihypertensive medications, and any medications that were considered an antidiabetic or antihypertensive medication based on medical judgment.

Prior and concomitant medications will be presented in a by-patient data listing by comorbidity type, ATC class and generic drug names, medication start date, and study drug dose level at time of medication start date. Concomitant medication will additionally be listed by comorbidity type, week on study, total daily dose and dose change from baseline.

9.7 Extent of Exposure and Study Drug Compliance

The duration of exposure will be presented in days and calculated as the date of last dose of study drug minus the date of first dose of study drug, plus one. The total actual dose received (mg) will be the sum of the actual dose administered for the duration of exposure. For patients where their dose received is either zero or missing, a received dose of zero is included in the total dose received derivation. Duration of exposure, total actual dose received (mg), and number of days at each dose level will be summarized using descriptive statistics in all patients and by comorbidity type. In addition, the number of patients reaching first, second, and third dose escalation, dose adjustment, highest dose level received, and the number of patients exposed at each dose level will be summarized by frequency counts and percentages overall and by comorbidity type.

Compliance to the study treatment regimen will be determined as the total actual number of capsules taken divided by the expected number of capsules taken, multiplied by 100. A patient is considered compliant to the treatment regimen if their compliance calculation is ≥ 80% of the prescribed dose. Expected capsules taken will be calculated as [(study drug stop date – study drug start date) + 1] multiplied by 4 (expected daily capsules taken). Dosing compliance will be summarized using descriptive statistics by comorbidity type and overall for the Safety Population. The number and percentages of patients who are < 80% compliant and ≥ 80% compliant within each comorbidity type group will be summarized.

9.8 Efficacy Analyses

Analysis of efficacy endpoints are described in Section 9.8.1 through Section 9.8.5. All efficacy data will be presented in by-patient data listings.

9.8.1 Primary Efficacy Endpoint

9.8.1.1 Primary Efficacy Endpoint for Patients with Uncontrolled Systolic Hypertension

For the hypertension subgroup of the ITT population, aligned to the clinical question of interest, the estimand of interest is the between-treatment difference in change in 24-hour average SBP from Baseline to Week 22 that is free from the confounding effect of rescue medication ("hypothetical") and regardless of whether or when the assigned treatment is discontinued ("treatment-policy").

Specifically, the estimand is the between-treatment difference between relacorilant and placebo in the change in 24-hour average SBP from Baseline to Week 22 in the population of patients with hypertension regardless of treatment discontinuation as if rescue medication was not available.

The primary efficacy analysis for the primary endpoint of change in 24-hour average SBP from Baseline to Week 22 will be performed using a linear mixed-model-for-repeated-measures (MMRM) using a placebo wash-out multiple imputation for treatment discontinuation and for

patients that use rescue medication. Restricted maximum likelihood (REML) estimation will be used.

The MMRM model will include Baseline 24-hour average SBP 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 following covariance structures will be used until the convergence criteria is met, in this order: unstructured covariance, heterogeneous compound symmetry, compound symmetry.

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

SAS statement that implements PROC MIXED will be used and the sample SAS code is presented in Appendix 2 and can be modified as needed. Estimated least squares means and 95% CIs for change from Baseline in 24-hour average SBP will be plotted by treatment and over time (from Baseline to Week 22).

The above-described analysis will be performed for mITT and PP populations as sensitivity analyses.

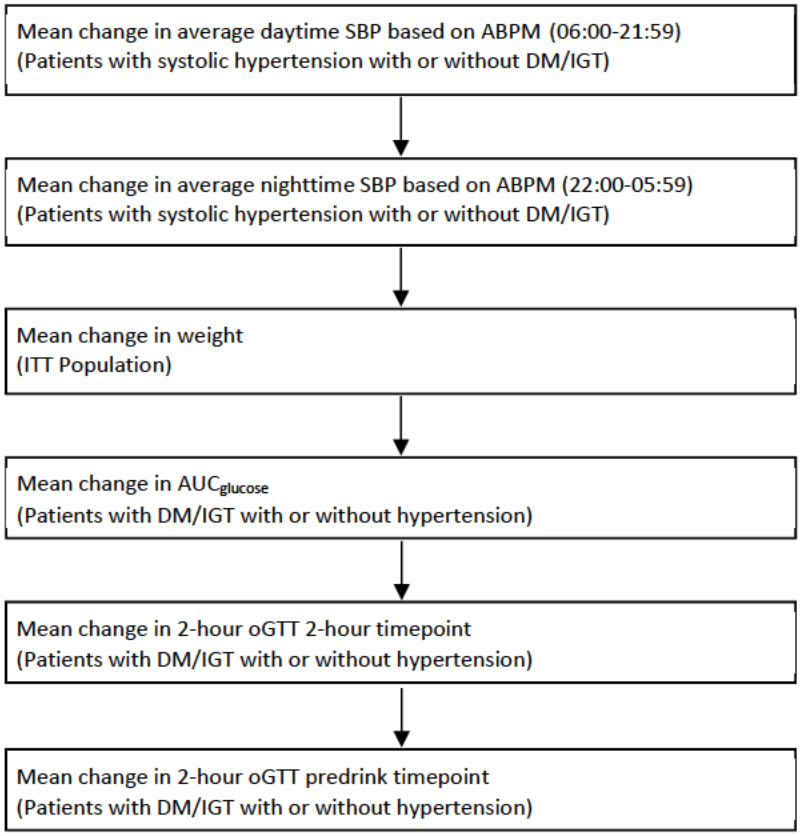
A sensitivity analysis to address mis-stratification at randomization will be performed using an MMRM model that includes Baseline 24-hour average SBP as a covariate; treatment, visit, and treatment by visit interaction, and stratification factor derived per electronic data capture (EDC) as fixed effects; patients within treatment groups as random effects. An unstructured covariance structure will be used to model within-patient error, and the Kenward Roger approximation will be used to model denominator degrees of freedom.

9.8.1.2 Multiplicity Adjustment for Analysis of Primary and Secondary Efficacy Endpoints

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

In order to provide experiment-wise 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.

9.8.1.3 Imputation for Primary Analysis

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. 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.

Missing data will be imputed by selecting random observations from a normal distribution centered at the value predicted by the regression model and with variance analogous to predicting a new observation. The imputation procedure will be iterated 100 times.

One hundred datasets will be generated, and an MMRM model with the factors and covariates will be run on each dataset. The point estimates and standard errors are computed, and the results are combined to yield a multiple imputation point estimate and standard error.

The analysis for the treatment difference will be based on an MMRM model with change from Baseline to Visit Week 22 as the dependent variable and the following covariate/factors:

- Treatment (with 2 levels, relacorilant and placebo).
- Visit (Scheduled), a categorical factor.
- Treatment-by-visit interaction.
- Baseline 24-hour average SBP, a continuous covariate.
- Stratification factor (with 2 levels, i.e., with or without DM/IGT).

The MMRM model will include patients within treatment arms as random effects. An unstructured covariance matrix will be used to model within-patient error. In case of convergence issues, the following covariance structures will be used until the convergence criteria is met, in this order: unstructured covariance, heterogeneous compound symmetry, compound symmetry. The Kenward and Roger method for calculating the denominator degrees of freedom for tests of fixed effects will be used.

This will constitute the data for the primary analyses.

9.8.2 Sensitivity Analysis for Primary Efficacy Endpoint

9.8.2.1 Analyses to Address Confounding by Rescue Medication and Early Discontinuation

To demonstrate the robustness of the primary analysis and to address the confounding by early discontinuation of treatment, the following supplementary analyses (Table 3) will be performed on the ITT population:

Table 3 Sensitivity Analyses for Primary Endpoint

	Sensitivity Analysis for Treatment Discontinuation and Rescue Medication
1	Placebo Wash-out Multiple Imputation Analysis (Section 9.8.2.1.1)
	Sensitivity Analysis for Treatment Discontinuation
2	Missing at Random (MAR) Analysis (Section 9.8.2.1.2)
3	Tipping Point Analysis (Section 9.8.2.1.3)

4	Multiple Imputation Analysis (Section 9.8.2.1.4)

9.8.2.1.1 Placebo Wash-out Multiple Imputation Analysis

For patients who use rescue medication or discontinue treatment early, a placebo wash-out multiple imputation will be used as a sensitivity analysis. All observed values regardless of treatment discontinuation or rescue medication use will be included in the analysis.

The 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.

One hundred datasets will be generated, and an MMRM model with the factors and covariates will be run on each dataset. The point estimates and standard errors are computed, and the results are combined to yield a multiple imputation point estimate and standard error.

The analysis for the treatment difference will be based on an MMRM model with change from Baseline to Visit Week 22 as the dependent variable and the following covariate/factors:

- Treatment (with 2 levels, relacorilant and placebo).
- Visit (Scheduled), a categorical factor.
- Treatment-by-visit interaction.
- Baseline 24-hour average SBP, a continuous covariate.
- Stratification factor (with 2 levels, i.e., with or without DM/IGT).

The MMRM model will include patients within treatment arms as random effects. An unstructured covariance matrix will be used to model within-patient error. In case of convergence issues, the following covariance structures will be used until the convergence criteria is met, in this order: unstructured covariance, heterogeneous compound symmetry, compound symmetry. The Kenward and Roger method for calculating the denominator degrees of freedom for tests of fixed effects will be used.

9.8.2.1.2 Missing at Random (MAR) Analysis

Mixed-effects model repeated measures (MMRM) analysis has an embedded missing at random (MAR) assumption that will estimate the mean for patients using the existing data for patients who discontinue early. As a supplementary analysis, the primary MRMM analysis (Section 9.8.1.1) will be performed using the embedded MAR assumption for patients who discontinue early for any reason. Missing data due to rescue medication will be imputed using a placebo wash-out multiple imputation.

9.8.2.1.3 Tipping Point Analysis

The assumption behind the tipping point analysis is that patients who drop out from the relacorilant arm would do worse after the drop-out and patients in the placebo arm would do better after drop-out than otherwise predicted by their observed outcomes and covariates. This pattern of missingness could be represented by a series of progressively more conservative shifts in the mean of missing values in each treatment arm (relacorilant and placebo) for 24-hour average SBP. The tipping point would correspond to the magnitude of the shift (denoted by δ_{1R} and δ_{1P} for relacorilant and placebo, respectively, in the description below) that reverses the study statistical conclusions from significant to nonsignificant. Combined with the clinical interpretation of the plausibility of the shifts, this approach would enable the assessment of the robustness of study conclusion to the differences between early discontinuations and completers.

We will implement this approach as follows:

- Impute missing values for Visit Week 22 using monotone regression-based multiple imputations with treatment and stratification factor included. This corresponds to the missing at random assumption (MAR) or a shift $\delta_{1R}=0$ and $\delta_{1P}=0$. A total of 100 imputed datasets will be created. For each imputed dataset, the same MMRM model specified in Section 9.8.1.1 will be used to estimate treatment effect on change in SBP from Baseline 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.
- At the next step, for patients with imputed values in the relacorilant and placebo arms, a pre-specified value $\delta_{1R}=2$ mmHg and $\delta_{1P}=0$ mmHg will be added to 24-hour average SBP. This will complete the generation of missing values at Visit Week 22 for this shift value.
- Steps 1-2 will be repeated for shift values in the range -6 to 6 mm Hg with increment of 2 mm Hg for δ_{1R} and δ_{1P} separately for one to consider as tipping points.
- The magnitude of the shifts for 24-hour average SBP at the tipping point will be evaluated for clinical relevance in the context of their plausibility for the difference between completers and patients who discontinued.

9.8.2.1.4 Multiple Imputation Analysis

Multiple imputation will be implemented to allow additional source of variability in the imputed values. A total of 100 imputed datasets will be created. Impute missing values due to early discontinuation from treatment for all scheduled visits up to visit Week 22 using monotone regression-based multiple imputation by treatment arm. Missing data due to rescue medication will be imputed using a placebo wash-out multiple imputation for the Week 22 visit after initiation of rescue medication (Section 9.8.1.3). SAS code example is listed in the Appendix 2. For each imputed dataset, the same MMRM model specified in Section 9.8.1.1 will be used to estimate treatment effect on change in SBP from Baseline to Week 22. The final estimate of treatment difference will be the average of the estimates based on the individual imputed datasets. The final estimate of the variance will be the average of the estimated variances based

on the individual imputed datasets (within-imputation variance) plus the sample variance of the estimated treatment differences based on the individual imputed datasets (between-imputation variance). The combination of individual estimates for treatment effect and the inference based on the combined estimate will be handled by SAS procedure MIANALYZE.

9.8.2.1.5 Sensitivity Analyses to Address Mis-stratification at Randomization

The MMRM model described in Section 9.8.1.1 will be repeated with sfactor being the correct stratification factor per EDC (with 2 levels, with or without DM/IGT), instead of the stratification factor at randomization in IRT.

9.8.2.1.6 Subgroup Analysis for Primary Efficacy Endpoints.

The MMRM model as described above in Section 9.8.1.1 will be performed on observed values for subgroups to investigate the consistency of the results. All subgroup mentioned in Section 6.6 and Section 6.7 will be performed for the primary endpoint if subgroup consists of 10 or more patients. A forest plot will be created including all the subgroup analysis results.

9.8.3 Secondary Efficacy Endpoints

9.8.3.1 Continuous Endpoints

Continuous secondary endpoints will be analyzed for the ITT population and mITT using a restricted maximum-likelihood (REML)–based linear MMRM analysis. The model will use visit as a fixed effect, and patient as a random effect. A compound symmetry covariance structure will be used to model the within-patient errors unless otherwise specified. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Least-squares means will be used to estimate the change from Baseline treatment effect at each visit, including Visit Week 22. The analysis using MMRM will be the main result. For endpoints collected only at the Week 22 or ET visit, ANCOVA model will be used for both Week 22 and last visit separately. In addition, the Wilcoxon signed-rank test (using observed data) will be used to evaluate if there is a significant change compared with Baseline at each visit in cases where departures from MMRM assumptions are noted.

Sample SAS code for the PROC MIXED procedure is presented in Appendix 2 and can be modified as needed.

9.8.3.1.1 Patients with DM/IGT: $AUC_{glucose}$ Based on oGTT Plasma Glucose

$AUC_{glucose}$ will be calculated based on results of the plasma 2-hour oGTT tests taken at Baseline, Week 2, Week 6, Week 10, Week 14, Week 18, and Week 22 for those patients with DM/IGT at study entry. At each visit, plasma 2-hour oGTT test includes glucose measurements at every half hour time-interval (pre-glucose drink and 0.5, 1, 1.5, and 2 hours after the glucose drink).

The AUC for such half hour time-interval will be calculated using the linear trapezoidal rule, as follows (where C_1 and C_2 are concentrations at times t_1 and t_2, respectively):

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

$AUC_{glucose}$ will be calculated as the sum of all-time intervals AUCs. Section 7.6.2.2 describes handling missing data for calculation of $AUC_{glucose}$.

For the DM/IGT subgroup of the ITT population, the estimand of interest is the between-treatment difference in $AUC_{glucose}$ from Baseline to Week 22 (estimated using a mixed model for repeated measures [MMRM] model).

The analysis for the primary endpoint of change in $AUC_{glucose}$ from Baseline to Visit Week 22 will be performed using a MMRM model on the DM/IGT subgroup of the ITT population. Restricted maximum likelihood (REML) estimation will be used.

The MMRM model will include Baseline $AUC_{glucose}$ 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 following covariance structures will be used until the convergence criteria is met, in this order: unstructured covariance, heterogeneous compound symmetry, compound symmetry. The Kenward and Roger method for calculating the denominator degrees of freedom for tests of fixed effects will be used when applicable to the covariance structure.

For this endpoint (change in $AUC_{glucose}$), a negative difference (relacorilant minus placebo) represents greater improvement for relacorilant-treated compared with placebo-treated patients.

In addition, $AUC_{glucose}$ will be summarized using descriptive statistics including two-sided 95% CI of the mean.

The above-described analysis will be performed for mITT and PP populations.

A sensitivity analysis to address mis-stratification at randomization will be performed using an MMRM model that includes Baseline $AUC_{glucose}$ as a covariate; treatment, visit, and treatment by visit interaction, and stratification factor derived per EDC as fixed effects; patients within treatment groups as random effects. An unstructured covariance structure will be used to model within-patient error, and the Kenward Roger approximation will be used to model denominator degrees of freedom.

9.8.3.1.2 Subgroup Analysis for $AUC_{glucose}$

The analysis for change from baseline in $AUC_{glucose}$ as described above in Section 9.8.1.1 will be performed for subgroups to investigate the consistency of the results. All subgroup mentioned in Section 6.6 and Section 6.7 will be performed for $AUC_{glucose}$ endpoint if subgroup consists of 10 or more patients. A forest plot will be created including all the subgroup analysis results.

9.8.3.1.3 Change in HbA1c from Baseline to Week 22 in Patients with DM/IGT

For patients in the ITT population with DM/IGT, the mean change in HbA1c from Baseline to Week 22 will be analyzed using an MMRM analysis. Additionally, in patients with DM, patients with IGT, patients with DM and HbA1c ≥ 6.5% at Baseline, and DM/IGT and HbA1c ≥ 5.7% at Baseline in the ITT population will be analyzed separately using an MMRM analysis.

The MMRM model will include Baseline HbA1c value 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 with parameters estimated by the REML estimation, and the Kenward-Roger approximation will be used to model denominator degrees of freedom.

Estimated least squares means and 95% CIs for change in HbA1c will be plotted by treatment and over time (from Baseline to Week 22).

The change from Baseline in HbA1c will also be analyzed by a Wilcoxon signed-rank test to evaluate if there is a significant change compared with Baseline at each visit up to Visit Week 22.

9.8.3.1.4 Change in Ambulatory Blood Pressure Monitoring from Baseline to Week 22 in Patients with Systolic Hypertension

Twenty-four-hour average SBP and DBP will be obtained by the patient at home using an ABPM. The mean change from Baseline to Week 22 in the 24-hour average SBP and DBP and HR will be analyzed using an MMRM analysis for systolic hypertension patients in the ITT population. Similarly, the mean change in the daytime and nighttime average SBP, DBP, and HR from Baseline to Week 22 will be analyzed using an MMRM analysis. 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 with parameters estimated by the REML estimation, and the Kenward-Roger approximation will be used to model denominator degrees of freedom.

Estimated least squares means and 95% CIs for change in 24-hour average SBP and DBP will be presented and plotted by treatment and over time (from Baseline to Week 22).

Two sets of Daytime and Nighttime windows will be applied:

- Definition1: Daytime (defined as 06:00 –21: 59) and Nighttime (defined as 22:00 – 05:59).
- Definition 2: Daytime (defined as 9:00 am to 9:00 pm) and Nighttime (defined as 1:00 am to 6:00 am).

For the subgroup of patients with systolic hypertension at Baseline in the ITT population, average ABPM measures will be summarized using descriptive statistics by visit, to include the change from Baseline. The change from Baseline will also be analyzed by a Wilcoxon signed-

rank test to evaluate if there is a significant change compared with Baseline at each visit up to Visit Week 22.

9.8.3.1.5 Change in Body Weight and Waist Circumference from Baseline to Week 22

For all patients in the ITT population, body weight and waist circumference will be summarized using descriptive statistics by visit, to include the change from Baseline. The change in body weight and waist circumference from Baseline to Week 22 will be analyzed separately using an MMRM analysis. 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 with parameters estimated by the REML estimation, and the Kenward-Roger approximation will be used to model denominator degrees of freedom.

Estimated least squares means and 95% CIs for change in body weight and waist circumference will be plotted by treatment and over time (from Baseline to Week 22).

Body weight and waist circumference will be summarized using descriptive statistics by visit, to include the change from Baseline for patients in the ITT population. The change from Baseline in body weight and waist circumference will also be analyzed by a Wilcoxon signed-rank test to evaluate if there is a significant change compared with Baseline at each visit up to Visit Week 22.

9.8.3.2 Endpoints Summarized with Proportions

For endpoints described as proportions for ITT and mITT population, the point estimate will be calculated including the 95% exact binomial two-sided CI (Clopper-Pearson). Risk differences between relacorilant and placebo will be evaluated using a logistic regression model including effects for treatment, continuous Baseline value, and stratification factor at randomization (Steingrimsson, 2017)

The risk difference and 95% CI for treatment will be reported. In case of logistic model convergence issues, Fisher's exact test will be used instead for evaluation of risk differences between treatment arms.

For analysis purposes, patients who discontinue treatment or take rescue medication will not be considered a responder.

9.8.3.2.1 Change in 2-hour oGTT glucose from Baseline to Week 22

In patients with IGT in the ITT population, the number and percentage of patients who achieved 2-hour oGTT glucose < 140 mg/dL at Week 22 will be summarized including the 95% exact binomial two-sided CI (Clopper-Pearson). Risk differences between relacorilant and placebo will be evaluated using a logistic regression model including effects for treatment, Baseline 2-hour

oGTT plasma glucose value, and stratification factor used at randomization (comorbidity status with 2 levels: DM/IGT only and both).

Separately, for patients with DM/IGT at Baseline and patients with DM at Baseline in the ITT population, the number and percentage of patients who achieved 2-hour oGTT glucose < 140 mg/dL at Week 22 will be summarized including the 95% exact binomial two-sided CI (Clopper-Pearson). Similarly, risk differences between relacorilant and placebo will be evaluated using a logistic regression model including effects for treatment, Baseline 2-hour oGTT plasma glucose value and stratification factor used at randomization (comorbidity status with 2 levels: DM/IGT only and both).

For analysis purposes, patients who discontinue treatment or take rescue medication will not be considered a responder.

9.8.3.2.2 Proportion of Patients with Decrease in AUCglucose from Baseline to Week 22

In patients with DM/IGT in the ITT population, the number and percentage of patients who achieved decrease of $AUC_{glucose}$ of ≥ 25%, ≥ 10%, ≥ 5% and any decrease will be summarized by visit including the 95% exact binomial two-sided CI (Clopper-Pearson). Risk differences between relacorilant and placebo will be evaluated using a logistic regression model including effects for treatment, Baseline $AUC_{glucose}$ value, and stratification factor used at randomization (comorbidity status with 2 levels: DM/IGT only and both).

For analysis purposes, patients who discontinue treatment or take rescue medication will not be considered a responder.

9.8.3.2.3 Change in HbA1c from Baseline to Week 22

In patients with HbA1c ≥ 6.5% at Baseline, the proportion of patients who achieved HbA1c < 6.5% by visit will be compared between treatment arms. The risk differences will be assessed using a logistic regression model including effects for treatment, Baseline HbA1c value and stratification factor used at randomization (comorbidity status with 3 levels: DM/IGT only, hypertension only, and both) in the ITT population. The number and percentage of patients with HbA1c ≥ 6.5% at Baseline who achieved HbA1c < 6.5% by visit will be presented along with a 95% exact binomial two-sided CI (Clopper-Pearson).

For analysis purposes, patients who discontinue treatment or take rescue medication will not be considered a responder.

9.8.3.2.4 Antidiabetic Medication and Antihypertensive medication

In patients with systolic hypertension at Baseline in the ITT population, the number and proportion of patients whose dose of antihypertensive medication decreased, discontinued, stayed the same, or switched/increased from Baseline to Week 22 and last modification due to worsening hypertension will be summarized, among those patients taking such medications at Baseline.

Separately, the difference between treatment arms in the proportion of patients with any decrease in antihypertensive medication due to improved blood pressure will be assessed by a logistic regression model including effects for treatment, and stratification factor used at randomization (comorbidity status with 2 levels: hypertension only and both) and Baseline average SBP for patients in the ITT population with systolic hypertension at Baseline. The proportion of patients in the ITT population with systolic hypertension at Baseline, for whom there is any decrease in antihypertensive medication due to improved blood pressure, along with the 95% exact binomial two-sided CI (Clopper-Pearson) will be presented.

Similarly, in patients with DM/IGT at Baseline in the ITT population, the number and proportion of patients whose dose of antidiabetic medication decreased, discontinued, stayed the same, or increased from Baseline to Week 22 and last modification due to worsening hyperglycemia will be summarized, among those patients taking such medications at Baseline.

Separately, the risk differences by treatment arm for patients with any decrease in dose of antidiabetic medication due to improved glucose control will be assessed by logistic model including effects for treatment, and stratification factor used at randomization (comorbidity status with 2 levels: DM/IGT only and both) and Baseline 2-hour oGTT. The proportion of patients in the ITT population with DM/IGT at Baseline, for whom there is any decrease in dose of antidiabetic medication due to improved glucose control, along with the 95% exact binomial two-sided CI (Clopper-Pearson) will be presented.

Differences in proportions between relacorilant and placebo will be evaluated using the stratified Cochran-Mantel-Haenszel (CMH) test and the estimated risk ratio and corresponding 95% CIs will be presented along with the 95% exact binomial two-sided CI (Clopper-Pearson). The stratification factor at randomization identifies hypertension patients with or without DM/IGT or DM/IGT patients with or without hypertension.

For analysis purposes, patients who discontinue treatment or take rescue medication will not be considered a responder. Additionally, if a new medication is started post-Baseline, this will be considered an increase in antihypertensive or anti-diabetic medication, respectively.

9.8.3.2.5 Change in Ambulatory Blood Pressure Monitoring from Baseline to Week 22

The proportion of patients in the ITT population with a reduction in the mean change from Baseline to Week 22, in 24-hour average SBP by 5 mm Hg (based on 24-hour ABPM) will be summarized separately. The risk difference between the treatment arms will be evaluated using a logistic regression model including effects for treatment, Baseline average SBP, and stratification factor used at randomization (comorbidity status with 2 levels: hypertension only and both hypertension and DM/IGT). The proportion of patients along with the 95% exact binomial two-sided CI (Clopper-Pearson) will be presented.

For analysis purposes, patients who discontinue treatment or take rescue medication will not be considered a responder.

9.8.3.2.6 Systolic Blood Pressure Normalization Analysis in Patients with Hypertension

In patients with uncontrolled hypertension at Baseline in the ITT population, the proportion of patients whose systolic blood pressure is normalized will be calculated. Patients whose systolic blood pressure normalized are defined as those patients whose 24-hour average SBP is less than 130 mm Hg at Week 22. The risk difference between the treatment arms will be evaluated using a logistic regression model including effects for treatment, Baseline 24-hour average SBP and stratification factor used at randomization (comorbidity status with 2 levels: hypertension only and both hypertension and DM/IGT). The number and percentage of patients in the ITT population with systolic hypertension at Baseline whose systolic blood pressure is normalized will be presented along with a 95% exact binomial two-sided CI (Clopper-Pearson).

For analysis purposes, patients who discontinue treatment or take rescue medication will not be considered a responder.

9.8.4 Exploratory Efficacy Endpoints

9.8.4.1.1 Body-Fat Composition by DXA

In all patients in the ITT population, changes in trabecular bone score, bone mineral density, and the percent and absolute amounts of total body and regional fat and lean tissue (whole body, trunk, and leg & arm) as measured by DXA scan will be summarized using descriptive statistics including two-sided 95% CI of the mean for Baseline, Week 22, last visit, as well as the change from Baseline. ANCOVA model will be used to evaluate the change in each parameter from Baseline to Week 22 and last visit separately. The ANCOVA model will include Baseline for the respective endpoint as a covariate; treatment, and stratification factor as fixed effects.

9.8.4.1.2 Change in ACTH Levels from Baseline to Week 22

For patients in the ITT population, the mean change in ACTH levels from Baseline to Week 22 will be analyzed using an MMRM analysis using PROC MIXED in SAS. Restricted maximum likelihood (REML) estimation will be used. The MMRM model will include Baseline ACTH value 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.

Estimated least squares means and 95% CIs for change in ACTH will be plotted by treatment and over time (from Baseline to Week 22).

The change from Baseline in ACTH levels will also be analyzed by a Wilcoxon signed-rank test to evaluate if there is a significant change compared with Baseline at each visit up to Visit Week 22/ET.

9.8.4.1.3 Change in Cholesterol Levels and Triglycerides from Baseline to Week 22

The change in total cholesterol, LDL cholesterol, VLDL cholesterol, and triglycerides from Baseline to Week 22 and Last visit will be analyzed separately using an ANCOVA Model for patients in the ITT population separately. The ANCOVA model will include Baseline value (for the respective endpoint) as a covariate; treatment, and stratification factor (at randomization) as fixed effects.

Total cholesterol, LDL cholesterol, VLDL cholesterol, and triglycerides will be summarized using descriptive statistics for Baseline, Week 22 and Last visit, as well as the change from Baseline for patients in the ITT population. The change from Baseline in each parameter will also be analyzed by a Wilcoxon signed-rank test to evaluate if there is a significant change compared with Baseline at each visit up to Visit Week 22 and Last Visit separately.

9.8.4.1.4 Change in Coagulation Markers from Baseline to Week 22

For patients in the ITT population, the change in Factor VIII, von Willebrand factor, protein S, protein C, TAT, platelets, and PTT from Baseline to Week 22 will be analyzed separately using an MMRM analysis. 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 with parameters estimated by the REML estimation, and the Kenward-Roger approximation will be used to model denominator degrees of freedom.

Estimated least squares means and 95% CIs for change in coagulation markers will be plotted by treatment and over time (from Baseline to Week 22).

Factor VIII, von Willebrand factor, protein S, protein C, TAT, platelets, and PTT will be summarized using descriptive statistics by visit, to include the change from Baseline for patients in the ITT population. The change from Baseline in each parameter will also be analyzed by a Wilcoxon signed-rank test to evaluate if there is a significant change compared with Baseline at each visit up to Visit Week 22/ET.

9.8.4.1.5 Change in DHEA-S from Baseline to Week 22

In all patients, DHEA-S will be summarized using descriptive statistics by visit, to include the change from Baseline. The change in each parameter from Baseline to Week 22/ET will be analyzed separately using an MMRM analysis. 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 with parameters estimated by the REML estimation, and the Kenward-Roger approximation will be used to model denominator degrees of freedom.

9.8.4.1.6 Change in Fasting Glucose from Baseline to Week 22 in Patients with DM

For patients in the ITT population with DM and HbA1c ≥ 6.5% at Baseline, the mean change in fasting glucose from Baseline to Week 22 will be analyzed using an MMRM analysis. The MMRM model will include Baseline fasting glucose value 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 with parameters estimated by the REML estimation, and the Kenward-Roger approximation will be used to model denominator degrees of freedom.

Estimated least squares means and 95% CIs for change in fasting glucose will be plotted by treatment and over time (from Baseline to Week 22).

The change from Baseline in fasting glucose will also be analyzed by a Wilcoxon signed-rank test to evaluate if there is a significant change compared with Baseline at each visit up to Visit Week 22/ET.

9.8.4.1.7 Change in Insulin Resistance Indices and Hyperglucagonemia

$AUC_{insulin}$, Matsuda Index, homeostatic model assessment of insulin resistance [HOMA-IR], and at selected visits $AUC_{glucagon}$ at Visit Week 22 will be analyzed using a REML-based linear MMRM model. The MMRM model will include Baseline for the respective endpoint as a covariate; treatment, visit, treatment by visit interaction, and stratification factor as fixed effects; and patients within treatment groups as random effects. An unstructured covariance structure will be used to model within-patient error, and the Kenward-Roger approximation will be used to model denominator degrees of freedom. The analysis for each of the endpoints will determine whether there is a difference between treatment groups in terms of change from Baseline to Week 22.

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

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

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

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

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

$$\frac{(g_0 + g_{0.5} * 2 + g_1 * 2 + g_{1.5} * 2 + g_2)}{8}$$

and

$$\frac{(i_0+i_{0.5}*2+i_1*2+i_{1.5}*2+i_2)}{8}$$

will be replaced with the mean of the observed data.

$AUC_{insulin}$ will be derived similar to $AUC_{glucose}$ (Section 9.8.1.1).

9.8.4.1.8 Cushing QoL and the Beck Depression Inventory®-II (BDI-II) Score

The Cushing QoL questionnaire is scored as a total score (ranging from 12 to 60), and is standardized to a scale from 0 (worst QoL) to 100 (best QoL) with the following formula:

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

The standardized total score will be used for analysis purposes.

Additionally, the scores for the questions "I have trouble sleeping", "My wounds take a long time to heal", and "I bruise easily" (questions 1, 3, and 4) of the Cushing QoL questionnaire will be summed for a physical problems subscale and the scores for the remaining questions (questions 2, 5, 6, 7, 8, 9, 10, 11, and 12) will be summed for a psychosocial issues subscale (Table 4). The subscales of the Cushing QoL are standardized with the following formula:

$$Y = \frac{(\mathrm{x} - \mathrm{L})}{(\mathrm{H} - \mathrm{L})} * 100.$$

where X is the total score of the subscale of interest, L is the lowest possible score of the subscale, and H is the highest possible score for the subscale. This equation transforms scores to a 0-to-100 scale, with 100 indicating the best possible QoL.

The mean change in Cushing QoL score, subscale in psychosocial issue, subscale in physical problems, and BDI-II score from Baseline to Week 22 will be analyzed separately using an MMRM analysis for patients in the ITT population. The MMRM model will include Baseline score 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 with parameters estimated by the REML estimation, and the Kenward-Roger approximation will be used to model denominator degrees of freedom.

Table 4 Items in Subscales of the Cushing QoL

Physical Problems Subscale
2. I have trouble sleeping
3. My wounds take a long time to heal
4. I bruise easily
Psychosocial Issues Subscale
2. I have pain that keeps me from leading a normal life
5. I am more irritable. I have sudden mood swings and angry outbursts
6. I have less self-confidence. I feel more insecure
7. I am worried about the changes in my physical appearance due to my illness
8. I feel less like going out or seeing relatives or friends
9. I had to give up my social or leisure activities due to my illness
10. My illness affects my everyday activities such as working or studying
11. It is for me to remember things
12. I am worried about my health in the future

In ITT patients, Cushing QoL scores and BDI-II scores will be summarized separately using descriptive statistics including two-sided 95% CI of the mean by visit, to include the change from Baseline. Where appropriate, Cushing QoL assessments and BDI-II scores will also be analyzed by a Wilcoxon signed-rank test to evaluate if there is a significant change compared with Baseline at each visit up to Visit Week 22/ET.

9.8.4.1.9 Other Continuous Exploratory Endpoints

For all patients in the ITT population, exploratory endpoints of the mean change from Baseline to Week 22 in sit-to-stand test score; trail making test scores, HPA-axis, morning and late-night salivary cortisol, and $AUC_{glucose}$ will be analyzed separately using an MMRM analysis for patients in the ITT population. The MMRM model will include Baseline score 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 with parameters estimated by the REML estimation, and the Kenward-Roger approximation will be used to model denominator degrees of freedom.

For all patients in the ITT population, exploratory endpoints of the mean change from Baseline to Week 22 and last Visit in serum osteocalcin, will be analyzed using an ANCOVA model for patients in the ITT population separately (visit). The ANCOVA model will include Baseline value (for the respective endpoint) as a covariate; treatment, and stratification factor (at randomization) as fixed effects.

9.8.5 Multicenter Studies

This is a multicenter study with sites across different regions expected to participate. A subgroup analysis is planned by region (United States vs. Rest of the World). The effect of study center on the efficacy analysis results may be explored post-hoc, as needed.

9.9 Pharmacodynamic Analysis

Pharmacodynamic (PD) endpoints and analysis methods will be described in a separate PD Analysis Plan that will be finalized before the database lock.

9.10 Pharmacokinetic Analysis

Intensive pharmacokinetic (PK) 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. PK endpoints and analysis methods will be described in a separate PK Analysis Plan that will be finalized before the database lock.

9.11 Safety Analyses

Safety variables will be analyzed for the Safety Population, defined as all patients who received at least 1 dose of study drug. All safety data will appear in by-patient data listings.

9.11.1 Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as those AEs with onset after the first dose of study drug or existing events that worsened after the first dose during the study and up to 28 days after the last dose of study drug. TEAEs will be summarized by treatment arm, and overall, unless otherwise specified.

Events reported with a partial onset date (e.g., month and year are reported but the day is missing) will be considered treatment-emergent if it cannot be confirmed that the event onset was prior to the first dose of study drug based on the available date entries.

Verbatim terms on case report forms will be mapped to preferred terms and system organ classes using MedDRA, version 26.0 or higher.

The Exposure Adjusted Incidence Rate (EAIR) for a TEAE is defined as:

$$Event\ Incidence\ rate\ per\ 100\ PYE = \frac{Total\ number\ of\ subjects\ with\ a\ event}{Total\ PYE} \times 100$$

The total patient-years-exposure (PYE) to a treatment is the sum of individual patient's PYE within the treatment exposure period and is defined as:

- For patients with an event within the exposure period:

$$PYE = (First\ event\ start\ date - first\ dose\ date + 1)/365.25$$

- For patients with no event within the exposure period:

$$PYE = (Last\ dose\ date - first\ dose\ date + 28)/365.25$$

Last dose date refers to the latest date of study treatment received in the study. If death occurs while dosing, PYE = death date -first dose date + 1.

The exact 95% CI based on Poisson distribution (Ulm, 1990) for EAIR is defined as:

$$\left(\frac{\chi^2_{2(Total\ number\ of\ patients\ with\ an\ event),0.025}}{2\times Total\ PYE}2, \frac{\chi^2_{2(1+Total\ number\ of\ patients\ with\ an\ event),0.975}}{2\times Total\ PYE}\right)\times 100,$$

where $\chi^2_{\nu,a}$ is the chi-square quantile for upper tail probability on ν degrees of freedom.

The exact 95% CI for difference of EAIR between two treatment arms will be calculated based on two independent Poisson distributions using below formula with point estimate of EAIR difference (IRD), $\widehat{IRD}$= n_1/PYE1 -n_2/PYE2,

$$x^2 = \left(n_1 - \frac{nPYE_1}{PYE}\right)^2 \Big/ \left(\frac{nPYE_1PYE_2}{PYE^2}\right)$$

and

$\widehat{IRD}\ CI = \widehat{IRD} \pm Z_{\alpha/2}\sqrt{\widehat{IRD}^2/x^2}$ where n = n_1 + n_2 with n_1 is the number of patients with event in treatment arm 1 and n_2 is number of patients with event in treatment arm 2, PYE = PYE_1 + PYE_2 with PYE_1 is patient-years-exposure in treatment arm 1 and PYE_2 is patient-years-exposure in treatment in treatment arm 2 and $Z_{\alpha/2}$ is a quartile of standard norm distribution with α = 0.05 (Sahai,1996).

Summaries that are displayed by system organ class (SOC) and preferred terms (PT) will be ordered by descending incidence of SOC and descending incidence of PT within each system organ class. Summaries displayed by PT only will be ordered by descending incidence of PT.

Tabular summaries with numbers and percentages of patients that have the following adverse events will be provided:

- Overview of TEAEs by treatment arm and overall
- Summary of TEAEs
  - By SOC and PT
  - By decreasing incidence of PT
  - By SOC, PT, and maximum severity

  - EAIR by SOC and PT
  - Crude risk difference by SOC and PT
  - By cumulative dose prior to the onset of the AE.
- Summary of TEAEs related to study drug by investigator assessment:
  - By SOC and PT
  - By decreasing incidence of PT
  - By SOC, PT, and maximum severity.
- Summary of treatment-emergent serious adverse events:
  - By decreasing incidence of PT
  - By SOC, PT, and maximum severity
  - EAIR by SOC and PT
  - Crude risk difference by SOC and PT
  - Related to study drug per investigator by SOC and PT
  - Related to study drug per investigator by decreasing frequency of PT
  - With action taken of permanent discontinuation of study drug by SOC and PT
  - With action taken of permanent discontinuation of study drug by SOC, PT, and maximum severity
  - With action taken of permanent discontinuation of study drug by PT
  - With action taken of permanent discontinuation of study by SOC and PT
  - With action taken of permanent discontinuation of study by SOC, PT, and maximum severity
  - With action taken of permanent discontinuation of study by PT
  - Leading to study drug dose change by SOC and PT (based on exposure CRF).
- Summary of TEAEs with action taken of permanent discontinuation of study drug:
  - By SOC and PT
  - By decreasing incidence of PT
  - By SOC, PT, and maximum severity.
- Summary of TEAEs with action taken of permanent discontinuation of study:
  - By SOC and PT
  - By decreasing incidence of PT
  - By SOC, PT, and maximum severity.
- TEAEs by PT occurring in at least 10% of the Safety Population by treatment arm, overall and by comorbidity type.
- TEAEs by SOC, PT, and maximum severity occurring in at least 10% of the Safety Population by treatment arm, overall and by comorbidity type.
- TEAEs by PT for PT with $\geq$ 5% of difference between treatment arms.

- TEAEs with fatal outcome by SOC and PT by treatment arm and overall.
- Grade 3 or higher TEAEs by SOC and PT.
- Grade 3 or higher TEAEs related to study drug by investigator assessment, by SOC and PT.
- TEAEs leading to dose reductions by SOC and PT by treatment arm and overall.
- TEAEs leading to dose interruptions by SOC and PT by treatment arm and overall.
- Summary of safety topics of interest listed in Section 9.11.2.

At each level of summarization (e.g., any AE, SOC, and PT), patients experiencing more than one AE will be counted only once. In the summary of TEAEs by severity grade, patients will be counted once at the highest severity reported at each level of summarization; in the summary of TEAEs by relationship, patients will be counted once at the closest relationship to study drug.

A subgroup analysis will be performed for overall TEAE table and TEAE by SOC and PT, and other key safety tables as applicable.

A butterfly plot of patient incidence of TEAEs occurring in at least 10% of the population by CTCAE grade and MedDRA PT will be presented.

Adverse event data will be presented in data listings. TEAEs, Serious TEAEs, TEAEs with action taken of permanent discontinuation of the study drug, TEAEs with action taken of permanent discontinuation of the study, TEAEs leading to dose reductions, TEAEs leading to dose interruptions, Grade 3 or higher TEAEs and TEAEs with fatal outcome will be presented in separate data listings.

Adverse events that are associated with infections due to SARS-CoV-2, including adverse events reported as COVID-19, will be listed separately to assess the impact of the 2020 pandemic on the results.

9.11.2 Special Safety Topics

A set of special safety topics were defined to identify and characterize events possibly associated with the use of relacorilant based on the mechanism of action, observed during the relacorilant pre-clinical and clinical development program, or are of clinical importance to the treated population. Summaries of these special safety topics will be produced to enhance the understanding of safety data.

Each special safety topic is a grouped clinical term comprising a broad set of AEs that are related patho-physiologically. The search methods used to identify the AEs grouped within each topic vary and may utilize an algorithmic approach or include one or more of the following: standardized MedDRA queries (SMQs), keyword searches of MedDRA PTs, and predefined lists of relevant PTs/SOCs. The search strategies used in analyses are specified in Appendix 3.

The special safety topics for this analysis include:

- Excessive glucocorticoid receptor (GR) antagonism
- Adrenal insufficiency

- Irregular vaginal bleeding associated with endometrial hypertrophy
- Peripheral edema
- Renal failure
- Arterial thromboembolisms
- Venous thromboembolisms
- Skin neoplasms
- Neoplasms (all)
- Cardiotoxicity
- Hepatotoxicity
- Anemia
- Thrombocytopenia
- Hemorrhage
- Peripheral Neuropathy
- Hyperkalemia
- New onset or exacerbation of pre-existing Hypertension
- Hypokalemia
- Hyperpigmentation
- Acne
- Hyperandrogenism in females
- Hypogonadism in males

9.11.3 Deaths

All deaths during the study, including the post-treatment follow-up period, will be summarized including the primary cause of death. A listing of all deaths reported will be provided.

9.11.4 Clinical Laboratory Tests

All descriptive summaries of laboratory results will be based on data analyzed by the central laboratory and presented in Système International (SI) units, as suggested by the Center for Biologics Evaluation and Research and the Center for Drug Evaluation and Research Position on Use of SI Units for Lab Tests (Clinical Data Interchange Standards Consortium. Standardized Lab Units, 2020).

All data will be included in by-patient data listings. Laboratory measurements identified as abnormal (i.e., outside the normal range) will also be listed separately by patient, study visit, dose at time of study visit, laboratory test, and unit.

Clinical laboratory measurements, including serum chemistry and hematology, will be summarized. Descriptive statistics will be presented for observed values and changes from Baseline to the last post-Baseline value.

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

- Shift from Baseline to the worst observed post-Baseline value within the treatment period per patient;
- Shift from Baseline to the last observed analysis visit value per patient.

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

Hematology and chemistry results for selected parameters will be assigned a toxicity grade based on the U.S. Department of Health and Human Services Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (National Cancer Institute-Common Terminology Criteria for Adverse Events, 2017), where applicable.

Grades will be presented as Grade 0, Grade 1, Grade 2, Grade 3, and Grade 4. Summary tables will be presented for each laboratory parameter to summarize the following:

- The worst observed post-Baseline CTCAE grade by treatment arm and overall.
- The last observed post-Baseline CTCAE grade by treatment arm and overall.

Summary results will include the count and percentage of patients by treatment arm and overall. A by-patient data listing for hematology and chemistry values with toxicity grade greater than or equal to Grade 3 will also be displayed.

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

9.11.5 Vital Signs

Vital sign parameter measurements, including BP, heart rate, respiratory rate, and oral body temperature, will be presented in listings and summarized. Descriptive statistics will be presented for results and change from Baseline to the last post-Baseline value by treatment arm and overall.

9.11.6 Electrocardiograms

Twelve-lead electrocardiograms (ECG) interval parameters will be presented in listings and summarized. Descriptive statistics will be presented for results and change from Baseline to the

last post-Baseline visit within treatment arm using the average of the duplicate readings per patient per visit for ITT population. Additionally, summaries of descriptive statistics will be provided separately by sex. The average of the triplicate readings at Screening will be used as Baseline.

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

9.11.7 Physical Examination

Results of the physical examination will be presented in by-patient listings including treatment, study visit, and body system. A listing of abnormal physical exam findings by visit and body system will be provided. The description of the abnormal finding and indication if the finding was clinically significant or not will be displayed.

9.11.8 Pregnancy Tests

Results of the pregnancy tests will be presented in by-patient listings including treatment and study visit.

10 CHANGES FROM PROTOCOL IN STUDY CONDUCT OR STATISTICAL ANALYSIS PLAN

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

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12 APPENDIX

APPENDIX 1

Propensity score approach will be used to impute missing data of SBP at Week 22 for patients who do not take rescue medication. The step-by-step methods are described below:

- Analysis will be performed for patients in the Hypertension subgroup of the ITT population.
- Within the same treatment arm, obtain the set of propensity scores from a logistic regression model, in which patient's status (Yes/No) of coming back for Week 22 assessment is regressed on observed Baseline characteristics including average 24-hour systolic and diastolic BP from ambulatory BP monitoring, comorbidity type (response to DM/IGT criteria, yes vs no), plasma ACTH, 24-hr UFC, late-night salivary cortisol, osteocalcin, age, body mass index (BMI), waist circumference, height, weight.
- Time on study treatment will also be a covariate in the model and will be in ahead of age and after osteocalcin for position of variable list included in the SAS model statement.
- One-to-one or pair matching will be implemented, and patients will be matched with quartiles of the propensity score within the same treatment arm.
- Impute missing values of average SBP at Visit Week 22 for patients who discontinue early, but do not come back for Week 22 measurement with the SBP values at Visit Week 22 from matched pair of patients.

APPENDIX 2

Example SAS code below will be used to conduct analyses described in Section 9.8.1.1.

```
ods output tests3=tests3 estimates=dsestimates lsmeans=dslsmeans convergencestatus=cstatus
           FitStatistics=cfit modelinfo=cinfo;
ods graphics on;

proc mixed data=mixed method=reml;

 class trt (ref= "0") visit (ref= "BL") sfactor usubjid;

 model aucchg = trt visit trt*visit sfactor base_auc/ ddfm=kenwardroger;

 repeated visit / type=un# subject=usubjid;

 estimate "Trt diff at BL"      trt 1 -1  trt*visit 1  0  0  0  0  0  0  -1   0   0   0  0  0  0/ cl;

 estimate "Trt diff at W22"   trt 1 -1  trt*visit 0  0  0  0  0  0  1  0   0   0   0  0  0  -1/ cl;

lsmeans trt*visit / cl;

run;
```

Go through the sequence of covariance structure as described in Section 9.8.1.1 if convergence criteria not met by using "un" option.

Example of SAS code for monotone regression in Section 9.8.2.1.1:

```
proc mi data=bpmi out=bpmi2 nimpute=100 seed=876453 minmaxiter=200;
        by trt01pn;
        class patstype;
        var patstype base week_2 Week_6 Week_10 Week_14 Week_18 Week_22 ;
        monotone regression;
run;
```

APPENDIX 3

Special Safety Topics

Topic	Definition	Search Methodology	Search Strategy
Excessive GR antagonism	A syndrome with severe (Grade 3 or higher) symptoms which is caused by excessive antagonism of the glucocorticoid receptor after treatment with a competitive antagonist.	Algorithm	Two or more of the following specified adverse events with temporal association (event onset +/- 2 days) and at least 1 has severity=Grade 3 or higher: • Fatigue • Decreased appetite • Nausea • Vomiting • Abdominal pain
Adrenal insufficiency	Deficiency of cortisol produced by the adrenal cortex that leads to under-stimulation of both the glucocorticoid receptor AND the mineralocorticoid receptor.	MedDRA HLT (Predefined PT list)	Adrenal cortical hypofunctions (HLT)
Irregular vaginal bleeding associated with endometrial hypertrophy	Vaginal bleeding in females, including menstruation, which is considered unusual for the patient and associated with endometrial thickening or hypertrophy.	Algorithm	One or more AE of the following specified AEs: Abnormal uterine bleeding, Dysmenorrhoea, Heavy menstrual bleeding, Menometrorrhagia, Polymenorrhagia, Polymenorrhoea, Intermenstrual bleeding, Abnormal menstrual clots AND One or more AE of the following specified AEs: Endometrial hypertrophy, Endometrial thickening
Peripheral edema	Fluid accumulation in the interstitial space.	Sponsor-defined PT list	Generalised oedema, Gravitational oedema, Localised oedema, Non-pitting oedema, Oedema, Oedema

Topic	Definition	Search Methodology	Search Strategy
			peripheral, Peripheral swelling, Fluid retention, Skin oedema, Swelling, Skin swelling
Renal failure	The inability of the kidneys to perform excretory function leading to retention of nitrogenous waste products from the blood	MedDRA HLT (Predefined PT list)	Renal failure and impairment (HLT)
Arterial thromboembolisms	Arterial occlusion from formation of localized blood clots or those that detach to occlude blood flow downstream.	MedDRA SMQ	Embolic and thrombotic events, arterial (SMQ)
Venous thromboembolisms	Venous occlusion from formation of localized blood clots or those that detach to occlude blood flow downstream.	MedDRA SMQ	Embolic and thrombotic events, venous (SMQ)
Skin neoplasms	Malignant and unspecified tumors and neoplasms related to the skin.	MedDRA SMQ	Skin malignant tumours (SMQ) (broad), Skin tumours of unspecified malignancy (SMQ) (broad)
Neoplasms (all)	Abnormal and excessive growth of cells in the body.	MedDRA SOC (Predefined PT list)	Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)
Cardiotoxicity	Toxicity that affects the heart (excluding thromboembolisms)	MedDRA SOC (Predefined PT list) and Sponsor-defined PT list	Cardiac disorders (SOC), or any PTs of: Ejection fraction decreased, Electrocardiogram abnormal, Electrocardiogram QT prolonged, Electrocardiogram QT interval abnormal
Hepatotoxicity	Toxicity that affects the liver	MedDRA SOC (Predefined PT list) and Sponsor-defined PT list	Hepatobiliary disorders (SOC), or any PTs of: Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood bilirubin increased, Gamma-glutamyltransferase increased, Hepatic enzyme increased,

Topic	Definition	Search Methodology	Search Strategy
			Liver function test abnormal, Liver function test increased, Transaminases increased
Anemia	A reduction in hemoglobin or hematocrit or red blood cell count	Sponsor-defined PT list	Anaemia, Haematocrit decreased, Haemoglobin decreased, Red blood cell count decreased
Thrombocytopenia	A reduction in platelet count	Sponsor-defined PT list	Thrombocytopenia, Platelet count decreased, Thrombocytopenic purpura, Mean platelet volume decreased
Hemorrhage	Loss of blood from a damaged blood vessel	MedDRA SMQ	Haemorrhage terms (excl laboratory terms) (SMQ)
Peripheral Neuropathy	Impairment of the peripheral motor, sensory and autonomic nervous system	MedDRA SMQ	Peripheral neuropathy (SMQ) (broad)
Hyperkalemia	Serum or plasma potassium concentration of more than 5.0 mEq/L caused by increased potassium intake, abnormal movement of potassium out of cells, or impaired potassium excretion.	Sponsor-defined PT list	Hyperkalaemia, Blood potassium increased
Hypokalemia	Serum or plasma potassium concentration of less than 3.0 mEq/L caused by a deficit in total body potassium stores, abnormal movement of potassium into cells, or increased potassium loss.	MedDRA SMQ	Hypokalaemia (SMQ) (narrow)
Hyperpigmentation	A condition in which the skin, hair, or nails has become darker in color	MedDRA HLT (Predefined PT list) and Sponsor-defined PT list	Hyperpigmentation disorders (HLT), or any PTs of: Pigmentation disorder, Gingival discolouration, Mucosal discolouration, Nail discolouration, Nail pigmentation, Nail disorder, Hair colour changes

Topic	Definition	Search Methodology	Search Strategy
New onset or exacerbation of pre-existing hypertension	Clinically significant increase in arterial blood pressure	MedDRA SMQ	Hypertension (SMQ) (narrow)
Acne	An inflammatory skin condition in which the pores of the skin are blocked.	Keyword search	Any PT containing: %acne%, %folliculitis%
Hyperandrogenism	The presence of an excess amount of androgens in females	Sponsor-defined PT list	Adrenal androgen excess, Hyperandrogenism, Hirsutism, Blood testosterone increased, Androgens increased, Blood androstenedione increased, Dihydrotestosterone increased, Amenorrhoea, Hypomenorrhoea, Menstruation delayed, Menstruation irregular
Hypogonadism	Deficiency of androgens in males	Sponsor-defined PT list	Adrenal androgen deficiency, Androgen deficiency, Feminisation acquired, Hypogonadism male, Blood testosterone decreased, Androgens decreased, Blood androstenedione decreased, Dihydrotestosterone decreased