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

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DOCUMENTATION OF STATISTICAL METHODS

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STATISTICAL ANALYSIS PLAN
STUDY CORT125134-455

Title	**Glucocorticoid Receptor Antagonism in the Treatment of Cushing Syndrome (GRACE): A Phase 3, Double-Blind, Placebo-Controlled, Randomized-Withdrawal Study of the Efficacy and Safety of Relacorilant**
IND Number	128625
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Indication	Cushing syndrome
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Protocol Version	Amendment 7 (17 May 2024) and Germany Amendment 5.1 (04 April 2023)
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APPROVAL SHEET

STATISTICAL ANALYSIS PLAN

CORT125134-455: Glucocorticoid Receptor Antagonism in the Treatment of Cushing Syndrome (GRACE): A Phase 3, Double-Blind, Placebo-Controlled, Randomized-Withdrawal Study of the Efficacy and Safety of Relacorilant

Reviewed and Accepted at Corcept Therapeutics by

[redacted]

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LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
ABPM	ambulatory blood pressure monitoring
ACTH	adrenocorticotropic hormone
AE	adverse event
ALT	alanine aminotransferase
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
CHM	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
EAIR	exposure adjusted incidence rate
ECG	electrocardiogram
eCRF	electronic case report form
ET	early termination
FDA	Food and Drug Administration
GR	glucocorticoid receptor

Abbreviation	Definition
HbA1c	hemoglobin A1c
HPA	hypothalamic-pituitary-adrenal
HR	heart rate
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)
IDMC	Independent Data Monitoring Committee
IGT	impaired glucose tolerance
IRT	Interactive Response System
ITT-OL	intent-to-treat analysis population in open-label phase
ITT-RW	intent-to-treat in randomized-withdrawal phase
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT-OL	modified intent-to-treat in open-label phase
mITT-RW	modified intent-to-treat in randomized-withdrawal phase
MMRM	mixed model for repeated measures
MRI	magnetic resonance imaging
mRNA	messenger RNA
oGTT	oral glucose-tolerance test
OL	open label
PD	pharmacodynamic
PK	pharmacokinetics
PP-OL	per-protocol analysis population in open-label phase
PP-RW	per-protocol analysis population in randomized-withdrawal phase
QoL	quality-of-life
REML	restricted maximum likelihood
ROW	rest of world
RW	randomized withdrawal

Abbreviation	Definition
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SI	Système International
TEAE	treatment-emergent adverse event
UFC	urinary free cortisol
US	United States
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 CORT125134-455.

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 CORT125134-455: Glucocorticoid Receptor Antagonism in the Treatment of Cushing Syndrome (GRACE): A Phase 3, Double-Blind, Placebo-Controlled, Randomized-Withdrawal Study of the Efficacy and Safety of Relacorilant. 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 database lock and 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; 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.

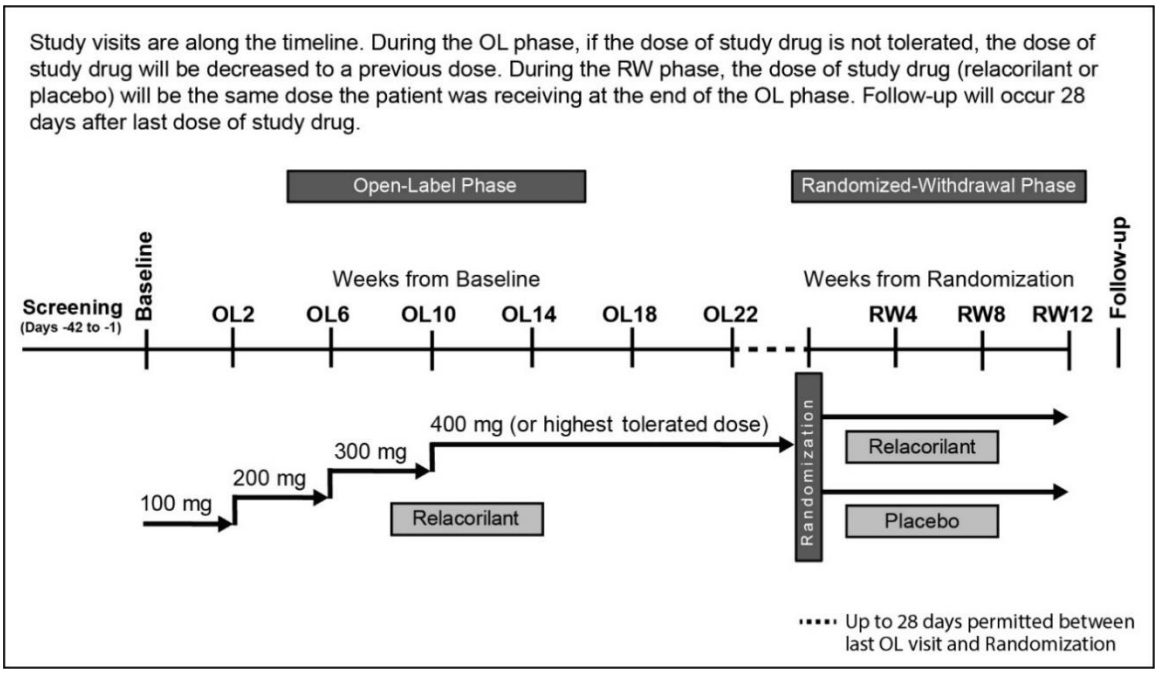
2 STUDY OVERVIEW

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

2.1 Overall Design

Study CORT125134-455 is a Phase 3, double-blind, placebo-controlled, RW study to assess the efficacy, safety and pharmacokinetics (PK) of relacorilant in patients with endogenous Cushing syndrome and concurrent diabetes mellitus (DM)/impaired glucose tolerance (IGT) and/or uncontrolled hypertension (Figure 1).

Figure 1 CORT125134-455 Study Design



The study phases are as follows:

Screening Phase

Up to 6 weeks to determine study eligibility.

Open-Label Phase (Baseline to Visit OL22)

Baseline is defined as Day 1 of the OL phase.

- The starting dose at Baseline will be 100 mg relacorilant once daily for 2 weeks.
- From Visit OL2 through Visit OL10, the dose of relacorilant will be increased every 4 weeks by 100 mg, as tolerated and based on improvement in signs and symptoms of

Cushing syndrome, to a target dose of 400 mg once daily (i.e., to 200 mg at Visit OL2, to 300 mg at Visit OL6, and to 400 mg at Visit OL10). Clinical benefit in the Open-Label Phase will be assessed by the Investigator either by a change from Baseline or change from the previous visit considering the following factors:
  - BP measurements and anti-hypertensive medications
  - Glucose levels and diabetes medication
  - Body weight and waist circumference
  - Cushingoid appearance and striae
  - Sit-to-stand test
  - Beck Depression inventory
  - Cushing Quality-of-Life questionnaire
- If all symptoms of Cushing syndrome present at Baseline have resolved, no dose escalation will occur beyond that visit.
- If any planned dose escalation is postponed, Visit OL14 can be used for a final dose escalation.
- Faster dose escalation during the open-label phase of the study for patients whose Cushing syndrome deteriorates may be allowed with medical monitor approval (not applicable in Germany).
- If access of patients to the study site is restricted due to the COVID-19 pandemic, dose escalation up to 200 mg may occur remotely if necessary. Subsequent dose escalations, however, are permitted only after completion of safety assessments.
- Dose interruption, reduction and re-escalation are permitted for safety/tolerability.
  - The relacorilant dose can be reduced to a previous dose if it is not tolerated
  - Re-escalation after a dose reduction is permitted until Visit OL18.

Randomized-Withdrawal Phase (Randomization to Visit RW12)

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

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

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

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

In patients with DM

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

In patients with IGT

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

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

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

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

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

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

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

Rescue criteria during the RW Phase

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

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

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

In the event of rescue medication use before Visit RW12:

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

3 STUDY OBJECTIVES

3.1 Primary Objectives

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

3.2 Secondary Objectives

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

4 STUDY ENDPOINTS

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

4.1 Primary Endpoint

The primary efficacy endpoint will be assessed in the RW phase. The study will be considered to have a positive outcome if the primary efficacy endpoint reaches statistical significance (Section 9.8.2.2):

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

4.2 Primary Safety Endpoints

- **In all patients**, assessment of safety based on TEAEs.

4.3 Secondary Efficacy Endpoints in the RW Phase

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

- In patients with DM/IGT, the mean change in $AUC_{glucose}$ from Visit OL22 to Visit RW12 as compared between relacorilant and placebo arms.
- In patients with DM/IGT, the mean change in HbA1c from Visit OL22 to Visit RW12, as compared between relacorilant and placebo.
- Comprehensive loss of response in DM/IGT subgroup with response at OL22: proportion of patients with a comprehensive loss of response with respect to hyperglycemic control from Visit OL22 to RW12, as compared between relacorilant and placebo arms, where the comprehensive loss of response is defined as follows:

In patients with DM:

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

OR

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

OR

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

In patients with IGT:

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

OR

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

4.4 Exploratory Efficacy Endpoints

Exploratory efficacy endpoints are listed below by study phase (RW or OL) and the type of endpoint.

4.4.1 Exploratory Efficacy Endpoints in the RW Phase

Continuous Endpoints

- Mean change from Visit OL22 to Visit RW12 in 24-hour average heart rate (HR) as compared between relacorilant and placebo (based on ABPM).
- Mean difference in daytime and nighttime average SBP, DBP, and HR (based on ABPM) at Visit RW12 as compared between relacorilant and placebo.

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

Endpoints Summarized with Proportions

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

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

4.4.2 Exploratory Efficacy Endpoints in the OL Phase

Continuous Endpoints

- In patients with uncontrolled hypertension, the mean change in SBP from Baseline to Visit OL22/ET.
- In patients with uncontrolled hypertension, the mean change in DBP from Baseline to Visit OL22/ET.
- Mean change in Cushing Quality-of-Life (QoL) score from Baseline to Visit OL22.
- Mean change in body-fat composition from Baseline to Visit OL22/ET, as determined by DXA.
- Mean change in the Beck Depression Inventory®-II (BDI-II) score from Baseline to Visit OL22/ET.
- Mean change in body weight from Baseline to Visit OL22/ET.
- In patients with IGT, the mean change in 2-hour plasma oGTT glucose from Baseline to Visit OL22/ET.
- In patients with DM (HbA1c ≥6.5% at Baseline), the mean change in HbA1c from Baseline to Visit OL22/ET.
- In patients with DM/IGT, the mean change in $AUC_{glucose}$ from Baseline to Visit OL22/ET.
- The mean change from Baseline to Visit OL22/ET in the following: waist circumference; lean mass measured by DXA; serum osteocalcin; the Beck Depression Inventory®-II (BDI-II) score; sit-to-stand test score; trail-making test score; sex-hormone levels (estradiol, total and free testosterone, sex-hormone–binding globulin,

follicle-stimulating hormone, and luteinizing hormone); urinary free cortisol (UFC), late-night salivary cortisol and plasma adrenocorticotropic hormone (ACTH); $AUC_{insulin}$, Matsuda Index, homeostatic model assessment of insulin resistance (HOMA-IR), and daytime and nighttime average blood pressure.

- In patients with adrenal Cushing syndrome (CS) (ACTH independent), the mean change in ACTH levels from Baseline to Visit OL22/ET.

Endpoints Summarized with Proportions

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

5 SAMPLE SIZE CONSIDERATION

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

This calculation assumes that enrolled patients will consist of approximately 25% with DM/IGT only, 25% with hypertension only, and 50% with both DM/IGT and hypertension at Screening. Attainment of the randomization targets within the hypertension subgroup in the RW phase further assumes that 75% of patients that present with hypertension only randomize to the RW phase and 20% of patients that present with both comorbidities (DM/IGT and hypertension) respond to hypertension criteria at Visit OL22 (hypertension only or DM/IGT and hypertension as described in Section 2.1) and randomize to the RW phase. This projected sample size will result in approximately 30 patients from the hypertension subgroup, and 16 patients from the DM/IGT and hypertension subgroup randomizing to the RW phase; thus, a total of approximately 46 patients meeting response criteria will be randomized into the hypertension subgroup.

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

Forty-six patients with hypertension (23 per treatment group with allocation ratio of 1:1) will ensure at least 90% power to detect the difference between placebo and treatment arms in proportion of patients with loss of response, assuming a loss of response in 25% of patients in the treatment arm and 75% in the placebo arm. These calculations are based on a Fisher's exact test of proportions at the α=0.05 two-sided significance level.

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

6 ANALYSIS POPULATION

6.1 Intent-to-Treat Analysis Population in Open-Label Phase (ITT-OL)

The intent-to-treat analysis population in open label phase (ITT-OL) will include all enrolled patients who received at least one dose of study drug. It will be used for analyses of exploratory efficacy endpoints in the OL phase.

6.2 Safety Population in Open-Label Phase (Safety-OL)

The Safety Population will include all enrolled patients who received at least one dose of study drug. It will be used for all safety analyses in the OL phase.

6.3 Modified Intent-to-Treat Analysis Population in Open-Label Phase (mITT-OL)

The modified intent-to-treat analysis population in open-label phase (mITT-OL) will include all patients in the ITT-OL population with at least one post-baseline efficacy assessment. It will be used for analyses of exploratory efficacy endpoints in the OL phase.

6.4 Per-Protocol Analysis Population in Open-Label Phase (PP-OL)

The per-protocol analysis population in open-label phase (PP-OL) will include all patients in the mITT-OL population who had no important protocol deviations that might impact the validity of the ABPM analysis. Patients in the PP-OL population who complete the OL phase without an important deviation will be used in sensitivity analyses of the exploratory efficacy endpoints in the OL phase.

6.5 Intent-to-Treat Analysis Population in Randomized-Withdrawal Phase (ITT-RW)

The intent-to-treat analysis population in randomized-withdrawal phase (ITT-RW) will include all patients who were randomized in the double-blind RW phase and received at least one dose of study drug post randomization. The ITT-RW population will be used for the analysis of the primary endpoint in the RW phase, as well as all secondary and exploratory efficacy endpoints.

6.6 Safety Population in Randomized-Withdrawal Phase (Safety-RW)

The Safety Population (Safety-RW) will include all patients who were randomized in the double-blind RW phase and received at least one dose of study drug post randomization. It will be used for all safety analyses in the RW phase.

6.7 Modified Intent-to-Treat Analysis Population in Randomized-Withdrawal Phase (mITT-RW)

The modified intent-to-treat analysis population in randomized-withdrawal phase (mITT-RW) will include all patients in the ITT-RW population with at least one post-randomization efficacy assessment for the primary efficacy endpoint (ABPM). The mITT-RW population will be used in sensitivity analyses for the analysis of the primary endpoint in the RW phase.

6.8 Per-Protocol Analysis Population in Randomized-Withdrawal Phase (PP-RW)

The per-protocol analysis population in randomized-withdrawal phase (PP-RW) will include all patients in the mITT-RW population who completed the study according to protocol specifications without an important deviation. The determination of the PP analysis population will be finalized prior to database lock and unblinding. Patients in the PP-RW population who complete the RW phase without an important deviation will be used in sensitivity analyses of the primary endpoint and the secondary efficacy endpoints in the RW phase.

6.9 ABPM Population

The ABPM analysis population will include all patients in the ITT-OL population who have ABPM results available at Baseline OL and Visit OL22, are randomized, have ABPM results available at Visit RW12 while on study drug and in whom compliance was acceptable (patient has at least 80% compliance [defined in Section 9.7] with prescribed dosing, by capsule counts, during OL and RW phases). The ABPM population will be used in sensitivity analysis of primary efficacy endpoint if at least 10 patients are included in this subgroup.

6.10 Key Subgroups

Key Subgroups in the Open-Label Phase

Cushing Syndrome Comorbidity Type:

- Patients with DM (fasting plasma glucose ≥126 mg/dL and/or 2-hour plasma oGTT glucose ≥200 mg/dL at 2 hours or HbA1c ≥6.5%), or impaired glucose tolerance (plasma glucose ≥140 mg/dL and <200 mg/dL on a 2-hour oGTT).
- Patients with uncontrolled hypertension (mean SBP ≥135 to ≤170 mm Hg and/or mean DBP ≥85 to ≤110 mm Hg based on 24-hour ABPM).

Key Subgroups in the Randomized-Withdrawal Phase

Cushing Syndrome Comorbidity Type by Response:

- DM/IGT subgroup of the ITT-RW population are patients with DM/IGT at Baseline OL that respond to DM/IGT criteria at Visit OL22 and are randomized to the RW phase.
- Hypertension subgroup of the ITT-RW population are patients with hypertension at Baseline OL that respond to hypertension criteria at Visit OL22 and are randomized to the RW phase.

6.11 Additional Subgroups

Additional Subgroups in the Open-Label Phase

Patients with uncontrolled hypertension at Baseline OL (mean SBP ≥135 to ≤170 mm Hg and/or mean DBP ≥85 to ≤110 mm Hg based on 24-hour ABPM):

- Treated with antihypertensive medications.
- Not treated with antihypertensive medications.

Patients with controlled hypertension at Baseline OL (mean SBP <135 mm Hg and mean DBP <85 mm Hg based on 24-hour ABPM) and medical history of hypertension:

- Treated with antihypertensive medications.
- Not treated with antihypertensive medications.

Patients with DM at Baseline OL:

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

DM or IGT subgroup at Baseline OL:

- Patients with IGT (plasma glucose ≥140 mg/dL and <200 mg/dL on a plasma 2-hours oGTT test).
- Patients with DM (fasting plasma glucose ≥126 mg/dL and/or 2-hour plasma oGTT glucose ≥200 mg/dL at 2 hours or HbA1c ≥6.5%).

Additional Subgroups in the Randomized-Withdrawal Phase

Patients with uncontrolled hypertension at Baseline OL in the ITT-RW population:

- Treated with antihypertensive medications.
- Not treated with antihypertensive medications.

Patients with controlled hypertension at Baseline OL in the ITT-RW population:

- Treated with antihypertensive medications.
- Not treated with antihypertensive medications.

DM/IGT subgroup of the ITT-RW population:

- DM at Baseline OL.
- IGT at Baseline OL.

Other subgroups of interest for the ITT-RW population:

- Patients with systolic hypertension at Baseline OL.
- Patients with diastolic hypertension at Baseline OL.

7 DEFINITIONS, COMPUTATIONS, AND CONVENTIONS

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

All statistical analyses detailed in this SAP will be conducted using SAS version 9.4 or higher. Additional validated software may be used to generate analyses, as needed.

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: Study day will be calculated in reference to the date of first dose of relacorilant in the OL phase (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.

Study day for efficacy in RW Phase (RW Day): Study day in RW phase will be calculated in reference to the date of Randomization (RW Day 1). For assessments conducted on or after the randomization date, study day is calculated as (assessment date - randomization date + 1). For assessments conducted before the randomization date, RW Day is calculated as (assessment date - randomization date). There is no RW Day 0.

Treatment-emergent period in OL Phase: The 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 but prior to date of the first dose of study drug in the RW phase. The treatment-emergent period will be used in the summaries of treatment-emergent adverse events (TEAEs).

Treatment-emergent period in RW Phase: The treatment-emergent period in RW phase is defined as the period of time from the date of the first dose of study drug in RW phase through 28 days after the last dose of study drug. The treatment-emergent period in RW phase will be used in the summaries of TEAEs presented by treatment arm for the RW phase.

7.1.1 Definitions of Baseline

7.1.1.1 OL Phase

The baseline for plasma 2-hours oGTT test is defined as the last oGTT corresponding time point measurement prior to first dose of study drug (e.g., pre-glucose drink, 0.5 hours post-glucose drink, 1-hour post-glucose drink, etc.) with enough timepoints to accurately calculate $AUC_{glucose}$. If no baseline exists with enough timepoints to accurately calculate $AUC_{glucose}$, then the last non-missing prior to treatment start date should be used. For example, the baseline for all post-baseline 0.5 hour post-glucose drink time points will be the last 0.5 hour post-glucose drink time point prior to first dose of study drug. In situations where a time point is missing in the oGTT

measurements, preference for baseline will be given to another visit occurring prior to first dose of study drug, if available, where all time points are non-missing (e.g., if a Day 1 oGTT time point is missing, and a Screening visit with no missing time points is available, that Screening visit will be flagged as baseline). If more than one alternative visit is available (scheduled or unscheduled), preference should be given to the last visit prior to first dose of study drug.

The baseline for the area under the concentration-time curve for glucose ($AUC_{glucose}$) is defined at the same visit (unscheduled or scheduled) that the plasma 2-hours oGTT test is defined.

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

The baseline for twelve-lead ECG interval parameters is defined as the average of the triplicate readings at Screening. The baseline for all other efficacy and safety parameters not previously mentioned is defined as the last measurement prior to first dose of study drug. The last visit prior to first dose of study drug may be an unscheduled or scheduled visit.

7.1.1.2 RW Phase

For patients who were randomized in the RW phase, the last measurement available prior to randomization date will be considered as the Baseline for the RW phase (Baseline RW).

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 are scheduled for collection based on the planned visit Study Day. If an unscheduled visit is mapped to a visit window that already has a non-missing assessment for the corresponding scheduled visit, the scheduled visit will be used in the analysis. Otherwise, if multiple visits occur within a single visit window, then the closest visit to the target day of the visit window will be used in the analysis. If there is a tie, the later visit will be used in the analysis.

The window for each study visit is relative to the Baseline or the Randomization visit. The acceptable visit window is ±3 days for Visits OL2, OL6, and OL10 and ±7 days for all other visits. The Randomization visit (the first day of the RW phase) may occur up to 28 days after Visit OL22 to allow time to obtain the required test results to evaluate eligibility for the RW phase. For the RW phase, the randomization day is considered Study Day 1. Table 1 and Table 2 outline the analysis visit windows.

Table 1 Analysis Visit Windows for Efficacy Assessments in OL Phase

Visit Name	Start Day	Target Day	End Day
Baseline		1	
OL2	2	15	29
OL6	30	43	57
OL10	58	71	85
OL14	86	99	113
OL18	114	126	140
OL22	141	155	162
ET		Study day of last dose of study drug	
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

Table 2 Analysis Visit Windows for Efficacy Assessments in RW Phase

Visit Name	Start Day	Target Day	End Day
Randomization		1	
RW4	2	29	43
RW8	44	57	71
RW12	72	84	91
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.
    - 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).
- Laboratory data will be reported using standard international (SI) and conventional units; as central laboratories are used for this study.
- 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). 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 WHODrug Global B3 March 1, 2020) 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 for OL phase will be presented in the order of comorbidity type (hypertension, DM/IGT, or DM/IGT and hypertension), patient identifier, and visit (or date of procedure or event, when applicable), unless stated otherwise.
- Listings for RW phase will be presented in the order of treatment arm, comorbidity type (hypertension, DM/IGT, or DM/IGT and hypertension), patient identifier, 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 at the beginning of OL phase 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, medical history, and prior/concomitant medications/procedures are provided in Section 7.6.4. and Cushing syndrome medical history in Section 7.6.5.

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 in OL phase, a summary of missing data at each of the visits will be provided. For endpoints in RW phase, such summary of missing data will be presented by treatment arm and by visit.

7.6.1 Handling Missing Data for Primary Efficacy Endpoint in RW Phase

7.6.1.1 Loss of Response with Respect to Hypertension Control

Patients who started rescue medication for hypertension before Visit RW12 or who discontinued study treatment prior to Visit RW12 (which are the intercurrent events for the purpose of this estimand) will be considered as non-responders in the primary analysis for loss of response in hypertension control. This is a composite strategy, per ICH E9[R1] 2021, integrating the occurrence of the intercurrent event into the variable and therefore no imputation for missing data is necessary. Furthermore, patients who do not use rescue medication or who do not discontinue treatment, but who have missing data at Visit RW12, will be considered non-responders.

7.6.2 Handling Missing Data for Secondary Efficacy Endpoints

7.6.2.1 Secondary Endpoints Summarized with Proportions

For endpoints that are defined as response to certain criteria, patients with missing data at Visit RW12 will be considered non-responders.

7.6.2.2 Continuous Secondary Efficacy Endpoints

7.6.2.2.1 Handling Missing Data for Hypertension Control (SBP/DBP)

As described in the protocol, if a patient discontinues early from the RW phase, the patient is instructed to return for Visit RW12 per the patient's original dosing schedule. Retrieved dropouts

are patients who discontinue study treatment prior to Visit RW12 and return for the Visit RW12 assessment of the SBP/DBP, as required by protocol.

Patients that discontinue study treatment after randomization and prior to Visit RW12, and do not return for the Visit RW12 assessment of the SBP/DBP, are referred to as 'non-retrieved dropouts'.

The missing data at Visit RW12 for non-retrieved dropouts will be imputed based on data from retrieved dropouts.

If fewer than 10 retrieved dropouts are available, then the primary analysis will use a placebo wash-out imputation method as described in Section 9.8.3.2.1. instead of the retrieved dropout approach.

In patients in the hypertension subgroup and randomized in the RW phase, imputation of missing data for the secondary endpoint of change in SBP/DBP from Visit OL22 to Visit RW12 will be performed depending on whether patient takes rescue medication:

- For patients who do not use rescue medication for hypertension before Visit RW12 (regardless if they discontinue treatment), all values for SBP/DBP including the Visit RW12, will be used in the analysis (including values from retrieved dropouts).
- For patients who do not take rescue medication for whom SBP/DBP at Visit RW12 is missing, only missing SBP/DBP values at Visit RW12 will be imputed based on data from retrieved dropouts, with similar baseline characteristics, within the same treatment arm. Details are provided in Appendix 1.
- For patients who use rescue medication for hypertension control (including potassium sparing diuretics) after randomization and before Visit RW12, the values collected after rescue medication is first used are irrelevant to the clinical question of interest, will not be used in the analysis. Such 'missing values' in SBP/DBP at Visit RW12 in patients that take hypertension rescue medication will be imputed using the placebo-based mean value (Mehrotra et al., 2017) calculated in patients who completed Visit RW12.

Additionally, a multiple imputation analysis based on placebo wash-out approach will be conducted to analyze the treatment effect of relacorilant compared with placebo.

In this study, the treatment effect is determined by loss of response with regards to hypertension criteria. In this context, the placebo 'wash-out' analysis means the missing SBP/DBP at Visit RW12 data will be imputed by considering a wash-out of the effect of treatment using completers in the placebo arm. Specifically, SBP/DBP data for patients on the placebo arm without measurements at Visit RW12 will be imputed using a monotone regression model based on observed SBP/DBP data of completers on the placebo arm with intermediate measurements, baseline SBP/DBP and stratification factor (as outlined in Section 9.8.3.2). For patients on the relacorilant arm, missing Visit RW12 data will be imputed using monotone regression model based on observed SBP/DBP data of completers on the placebo arm with baseline SBP/DBP and stratification factor.

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 data sets will be generated and an MMRM with the factors and covariates (as described in Section 9.8.3.2.1) will be run on each data set and point estimates and standard errors computed and the results combined to yield a multiple imputation point estimate and standard error.

7.6.2.2.2 Handling Missing Data for the Purpose of Calculating $AUC_{glucose}$

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

- If the pre-glucose drink time point or 30-minute post-glucose drink time point is 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 the 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 the associated oGTT pre-glucose drink to 90-minute post-glucose drink values and AUC will be used in the summary tables.
    - Otherwise, observed values only will be used.

Handling Missing Data in RW Phase for $AUC_{glucose}$

As described in the protocol, if a patient discontinues early from the RW phase, the patient is instructed to return for Visit RW12 per the patient's original dosing schedule. Retrieved dropouts are patients who discontinue study treatment prior to Visit RW12 and return for the Visit RW12 assessment of the oGTT, as required by protocol.

Patients that discontinue study treatment after randomization and prior to Visit RW12, and do not return for the Visit RW12 assessment of the oGTT, are referred to as 'non-retrieved dropouts'.

The missing data at Visit RW12 for non-retrieved dropouts will be imputed based on data from retrieved dropouts.

If fewer than 10 retrieved dropouts are available, then the analysis will use a placebo wash-out imputation method as described in Section 9.8.3.4.1 instead of the retrieved dropout approach.

Among patients in the DM/IGT subgroup who are randomized in the RW phase, imputation of missing data for the secondary endpoint of change in $AUC_{glucose}$ from Visit OL22 to Visit RW12 will be performed depending on whether the patient takes rescue medication:

- For patients who do not use rescue medication for DM/IGT before Visit RW12 (regardless of if they discontinue treatment), all values for $AUC_{glucose}$ including the Visit RW12, will be used in the analysis (including values from retrieved dropouts).
- For patients who do not take rescue medication for whom $AUC_{glucose}$ at Visit RW12 is missing, only missing $AUC_{glucose}$ values at Visit RW12 will be imputed based on data from retrieved dropouts, with similar baseline characteristics, within the same treatment arm. Details are provided in Appendix 1.
- For patients who use rescue medication for hyperglycemia control after randomization and before Visit RW12, the values collected after rescue medication is first used are irrelevant to the clinical question of interest, and thus will not be used in the analysis. Such 'missing values' in $AUC_{glucose}$ at Visit RW12 in patients who take diabetes rescue medication will be imputed using the placebo-based mean value (Mehrotra et al., 2017) calculated in patients who completed Visit RW12.

Additionally, a multiple imputation analysis based on placebo wash-out approach will be conducted to analyze the treatment effect of relacorilant compared with placebo.

In this study, the treatment effect is determined by loss of response with regards to response to DM/IGT criteria. In this context, the placebo 'wash-out' analysis means the missing $AUC_{glucose}$ at Visit RW12 data will be imputed by considering a wash-out of the effect of treatment using completers in the placebo arm. Specifically, $AUC_{glucose}$ data for patients on the placebo arm without measurements at Visit RW12 will be imputed using a monotone regression model based on observed $AUC_{glucose}$ data of completers on the placebo arm with intermediate measurements, baseline $AUC_{glucose}$ and stratification factor (as outlined in Section 9.8.3.4). For patients on the relacorilant arm, missing Visit RW12 data will be imputed using monotone regression model based on observed $AUC_{glucose}$ data of completers on the placebo arm with baseline $AUC_{glucose}$ and stratification factor.

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 data sets will be generated and an MMRM with the factors and covariates (as described in Section 9.8.3.4.1) will be run on each data set and point estimates and standard errors computed and the results combined to yield a multiple imputation point estimate and standard error.

7.6.3 Handling Missing Data for Exploratory Efficacy Endpoints

For calculations involving exploratory efficacy endpoints in RW phase, the same rules for handling missing data as described for secondary efficacy endpoints in RW phase (Section 7.6.2) will be applied. For continuous exploratory efficacy endpoints collected in the RW phase, all efficacy by-visit analyses will include summaries of observed cases only, where no imputations will be used, except for the hypertension control (Section 7.6.2.2.1) and AUC missing data handling rules (Section 7.6.2.2.2).

7.6.3.1 Handling Missing Data for Efficacy Endpoints in the Open-Label Phase

7.6.3.1.1 Endpoints from OL Phase Summarized with Proportions

For the purpose of analyzing endpoints that are defined as response to certain criteria, patients with missing data at Visit OL22 will be considered non-responders.

7.6.3.1.2 Continuous Endpoints from OL Phase

For continuous exploratory efficacy endpoints collected in the OL phase, all efficacy by-visit analyses will include summaries of observed cases only, where no imputations will be used except for AUC as described below:

For calculations involving AUC based on plasma 2-hours oGTT test in the OL phase, the same rules for handling missing data as described in (Section 7.6.2.2.2) will be applied at individual timepoints:

- 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 the available data. For example, if the 90-minute time point is missing, a larger trapezoid will be constructed to connect the 60-minute and 120-minute time points.
- If only the 120-minute post-glucose drink time point is missing, the AUC will be calculated using the available data, and the associated oGTT pre-glucose drink to 90-minute post-glucose drink values and AUC will be used in the summary tables.
    - Otherwise, observed values only will be used.

7.6.4 Handling Incomplete or Missing Dates for Adverse Events, Medical History 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 Month is missing and Day is non-missing, treat as both Month and Day are missing.
- 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.

Medical history start and end dates will follow the same imputation as adverse events for partially missing dates.

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 Cushing Syndrome Medical History

If the diagnosis date of Cushing syndrome 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 syndrome 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 during RW phase for the purposes of early stopping of the study or modifying the study design. However, during OL phase 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 database lock.

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 M2ectd 2003).

9.2 Patient Disposition

Screen failure information is collected in an interactive web response system (IWRS), not on the eCRF, and it will not be incorporated into the Study Data Tabulation Model (SDTM) database.

Patient disposition will be summarized for the ITT population by OL phase and RW phase.

Participant disposition during OL phase will present the number of patients enrolled, number treated with study drug, and among those number of patients who completed OL phase and who discontinued from OL phase, study treatment and reasons for discontinuation. Primary reason for discontinuation of treatment, including any of the following, will be summarized:

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

Participant disposition during RW phase will present the number of patients randomized, treated with study drug, completed the RW phase and who discontinued from RW phase, discontinued early the study treatment in the RW phase and reasons for discontinuation. Frequency counts and percentages of patients who complete the study and those who discontinue early for any of the following reasons will also be calculated:

- Adverse Event
- Lost to Follow-up
- Pregnancy
- Study Terminated by Sponsor
- Lack of Efficacy
- Withdrawal by Patient
- Physician Decision

- Death
- Non-Compliance with study drug
- Protocol Deviation
- Other

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

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

Attendance at scheduled visits will be shown as the number of patients who completed each scheduled visit for both OL phase and RW phase. The time (in days) from OL22 to randomization and initiation of treatment in RW phase will be summarized.

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 by OL/RW phases, 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. Additionally, COVID-19 related protocol deviations will be presented in separate listings.

9.4 Demographic Characteristics and Baseline Characteristics

The following demographic characteristics will be presented in listings and summarized in ITT-OL Analysis Population and ITT-RW Population (by treatment arm and overall):

- Age at beginning of OL phase
- Sex
- Ethnicity
- Race
- Geographic region: North America (United States and Canada) and ROW (Austria, Bulgaria, Germany, Israel, Italy, Netherlands, Poland, Romania, and Spain)
- Age (three levels <45 vs. [45, 65) vs. ≥65)

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

Baseline characteristics include height, weight, body mass index (BMI), waist circumference, plasma ACTH, 24-hr UFC, late-night salivary cortisol, plasma 2-hour oGTT test, $AUC_{glucose}$, HbA1c, and mean 24-hour SBP and DBP from ABPM. BMI will be calculated as: weight (kg) / [height (cm) / 100]^2.

Demographics and baseline characteristics will be summarized for the ITT-OL and ITT-RW populations, including by comorbidity subgroups (DM/IGT and hypertension) in each of the analysis populations. Baseline characteristics will also be summarized by Cushing's etiology (adrenal vs pituitary, i.e., ACTH independent vs ACTH dependent).

9.5 Medical History

Medical history will be presented in listings and summarized for all patients in the ITT-OL and ITT-RW, and presented by comorbidity type (DM/IGT or hypertension), and overall. Continuous variables at baseline will be summarized using descriptive statistics. Frequency counts and percentages to summarize patients reporting medical history by system organ class (coded using MedDRA version 26.0) and Cushing syndrome history will be presented. Time (months) since diagnosis of Cushing syndrome will be calculated as the informed consent date minus the diagnosis date from the medical history eCRF and will be summarized using descriptive statistics.

9.6 Prior and Concomitant Medications

Medications will be coded using the World Health Organization (WHO) Drug Global B3 version March 1, 2023 or later. Medications entered on the eCRF will be mapped to ATC drug class (level 4) and drug name. Prior and concomitant medications will be summarized in the Safety Population for both OL phase and RW phase.

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 (DM/IGT or hypertension), and all patients combined, as will the number and percentage receiving any medication by ATC drug class and generic drug name. For all concomitant medications table summaries, the number and percentage of patients receiving any medication will be summarized by study drug dose category, comorbidity type (DM/IGT or hypertension), and all patients combined, as will the number and percentage receiving any medication by ATC drug class and generic drug name. Additionally, a summary table of the number and percentage of patients receiving any medication by ATC drug class will be presented. The study drug dose category each concomitant medication is assigned to will be determined by the medication start date. Patients reporting use of more than one medication at each level of summarization (any medication received, ATC class, and generic drug name) will be counted only once. ATC class terms will be displayed by descending order of incidence, as will generic drug names within each ATC class. 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 for both OL phase and RW phase; and
- Medications used to treat diabetes or hypertension for patients in the Safety Population for both OL phase and RW phase.

Tables summarizing reduction in antidiabetic, antihypertensive, and antidepressant 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 OL, median total daily dose at Baseline OL, number of patients with a dose reduction, median reduction in total daily dose at last visit, the number of patients with any reduction in daily dose, the number of patients with ≥25% reduction in daily dose, the number of patients with ≥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. Any dose increase or new use of a mineralocorticoid antagonist (as defined in Appendix 4) during the study, for the treatment of either hypertension or hypokalemia, will be regarded as antihypertensive medication.

Prior and concomitant medications will be presented in a by-patient data listing by comorbidity type (DM/IGT or hypertension), 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 (DM/IGT or hypertension), 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. 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 by study phase (OL and RW) and by comorbidity type. In addition, for the OL phase, the number of patients reaching first, second, and third dose escalation, 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 (DM/IGT or hypertension).

Relative dose intensity will be reported. Relative dose intensity is calculated for each visit interval (e.g., Baseline to OL2, OL2-OL6, etc.) as the total dose received divided by the total dose expected between visits, multiplied by 100, for the particular visit interval and overall by phase.

Compliance to the study treatment regimen will be determined as the total actual dose received divided by the expected dose received, multiplied by 100. A patient is considered compliant to the treatment regimen if their compliance calculation is ≥80% of the prescribed dose. Expected dose received will be calculated as [(study drug stop date – study drug start date) + 1] multiplied by expected daily dose and will reflect dose escalation for each patient as entered in the eCRF. Dosing compliance will be summarized using descriptive statistics by study phase (OL and RW) overall and by comorbidity type (DM/IGT or hypertension), based on the Safety Population. The number and percentages of patients who are <80% compliant and ≥80% compliant within each comorbidity type group will be summarized.

Extent of exposure and compliance will be reported in the Safety population in OL and RW phase and within each comorbidity type.

9.8 Efficacy Analyses

Analysis of efficacy endpoints are described in Section 9.8.2 through Section 9.8.4. All efficacy data will be presented in by-patient data listings.

9.8.1 Multiple Comparisons/Multiplicity Adjustment

The primary efficacy analysis will be the comparison between relacorilant and placebo arms in the proportion of patients with a loss of response with respect to hypertension from Visit OL22 to Visit RW12 based on 24-hour ABPM. The Type I error rate will be controlled at a 2-sided 0.05 level for the primary efficacy analysis.

In patients with hypertension at study entry, the proportion of patients with a loss of response with respect to hypertension from Visit OL22 to Visit RW12 based on 24-hour ABPM is defined as follows:

- In patients who met only the SBP response criterion, an increase in SBP ≥5 mm Hg.
- In patients who met only the DBP response criterion, an increase in DBP by ≥5 mm Hg.
- In patients who met both the SBP and DBP response criteria, an increase in either SBP or DBP by ≥5 mm Hg.
- Any increase or modification in antihypertensive medication due to worsening hypertension.
- Patients discontinue treatment in RW phase for any reason.

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

9.8.2 Primary Efficacy Endpoint

9.8.2.1 Loss of Response with Respect to Hypertension Control in RW Phase

For patient in the hypertension subgroup of the ITT-RW population, aligned to the clinical question of interest, the estimand of interest is the difference between proportions of patients losing response with respect to hypertension control, between treatment arms from Visit OL22 to

Visit RW12 that is free from the confounding effect of rescue medication regardless of whether or when the assigned treatment was discontinued.

Specifically, the estimand is difference in proportion of patients losing response between (continuing) relacorilant and placebo (withdrawing relacorilant) treatment in patients with initial response to relacorilant.

For patient with hypertension at study entry, loss of response from Visit OL22 to Visit RW12 based on 24-hour ABPM is defined as follows:

- In patients who met only the SBP response criterion, an increase in SBP ≥5 mm Hg.
- In patients who met only the DBP response criterion, an increase in DBP by ≥5 mm Hg.
- In patients who met both the SBP and DBP response criteria, an increase in either SBP or DBP by ≥5 mm Hg.
- Any increase or modification in antihypertensive medication due to worsening hypertension.
- Patients discontinue treatment early for any reason (prior to Visit RW12).

The proposed estimand for hypertension control in the hypertension subgroup of the ITT-RW population follows a composite strategy with respect to early discontinuation and use of rescue medication.

9.8.2.2 Primary Efficacy Endpoint for Patients with Uncontrolled Hypertension

For the hypertension subgroup of the ITT-RW analysis population, the primary analysis will determine whether there is a difference between treatment groups in terms of the proportion of patients with a loss of response with respect to hypertension from Visit OL22 to Visit RW12 based on 24-hour ABPM. This will be accomplished by using the logistic regression model,

$$\log\frac{p}{1-p} = \beta_0 + \beta_1 \times treatment + \beta_2 \times sfactor$$

where *treatment* is the treatment arm (with 2 levels, relacorilant and placebo) and *sfactor* is the stratification factor at randomization in IRT (with 2 levels, with or without DM/IGT). The coefficients β_0 indicates the intercept, β_1 indicates the regression coefficient for treatment and β_2 indicates the regression coefficient for stratification factor. The exp(β_1) is the odds ratio (OR) that estimates the association between treatment and proportion of patients with a loss of response.

The chi-square test statistic and p-value will be used to test the below null hypothesis,

$$H_0: \beta_1 = 0 \ \ versus \ \ H_1: \beta_1 \neq 0$$

The parameter estimates and standard errors, the chi-square test statistics and p-values, along with the odds ratios and 95% CI will be reported (Steingrimsson et al. 2017). In case of logistic model convergence issues, Fisher's exact test will be used instead.

For this endpoint (proportion of patients with loss of response), OR<1 represents lower odds of loss of response under treatment with relacorilant compared with treatment with placebo, in the RW phase.

In addition to the primary analysis described above, the proportion of patients with a loss of response will be summarized for both relacorilant and placebo arms together with corresponding two-sided 95% CI using Clopper-Pearson method in the hypertension subgroup of the ITT-RW population.

9.8.2.3 Sensitivity Analysis for Primary Efficacy Endpoint

9.8.2.3.1 Sensitivity Analyses to Address Confounding by Early Discontinuation

To demonstrate the robustness of the primary analysis, the following sensitivity analyses (Table 3) will be performed on the ITT-RW population:

Table 3 Sensitivity Analyses for Loss of Response in Patients with Hypertension

	Sensitivity Analysis
1	Retrieved Dropout Imputation (Section 9.8.2.3.1.1)
2	LOCF Analysis (Section 9.8.2.3.1.2)

9.8.2.3.1.1 Retrieved Dropout Imputation Sensitivity Analysis for Uncontrolled Hypertension

If 10 or more discontinued patients return for Visit RW12 and their retrieved dropout data are available, then for patients who discontinue early for whom loss of response in hypertension control at Visit RW12 cannot be determined due to missing data, SBP/DBP Visit RW12 data will be imputed based on data from retrieved dropouts, with similar baseline characteristics, within the same treatment arm. Those patients who have any increase or modification in antihypertensive medication due to worsening hypertension will be considered a loss of response. The analysis for patients with loss of response to hypertension control as described in Section 9.8.2.2 will be performed with the imputed values.

9.8.2.3.1.2 LOCF Sensitivity Analysis for Uncontrolled Hypertension

Additionally, for patients who discontinued early for any reason, the last non-missing observation prior to the patient discontinuing treatment will be carried forward to impute the missing value for Visit RW12. With the LOCF imputed values, loss of response from Visit OL22 to Visit RW12 based on 24-hour ABPM is defined as follows:

- In patients who met only the SBP response criterion, an increase in SBP ≥5 mm Hg.
- In patients who met only the DBP response criterion, an increase in DBP by ≥5 mm Hg.
- In patients who met both the SBP and DBP response criteria, an increase in either SBP or DBP by ≥5 mm Hg.
- Any increase or modification in antihypertensive medication due to worsening hypertension.

The proportion of patients with a loss of response will be calculated for both relacorilant and placebo arms together with corresponding two-sided 95% CI using Clopper-Pearson method.

The logistic regression model analysis for patients with uncontrolled hypertension as described in Section 9.8.2.2 will be performed for the loss response using LOCF values.

9.8.2.3.2 Sensitivity Analyses to Address Mis-stratification at Randomization

The logistic regression model described in Section 9.8.2.2 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.

9.8.2.4 Supplementary Analyses for Primary Efficacy Endpoint in Subgroups

Analysis described above in Section 9.8.2.1 through Section 9.8.2.2 will be performed for mITT-RW population, PP-RW population and subgroups to demonstrate the robustness of the results. The following subgroup analyses (Table 4) will be considered:

Table 4 Subgroup Analyses for Loss of Response In Patients with Hypertension

Subgroup Analysis	Analysis Population/Subgroups
1	mITT-RW
2	ITT-RW (by DM/IGT Subgroup within patients with hypertension)
3	ABPM analysis population
4	PP-RW
5	ITT-RW (by Region - North America vs. ROW)
6	ITT-RW (by Age Group - <45 vs. [45, 65) vs. ≥65)
7	ITT-RW (by Sex - Male vs. Female)
8	ITT-RW (by antihypertensive medications - Treated vs. Not Treated)

All subgroup analyses mentioned in Table 4 will be performed if the subgroup consists of 10 or more patients.

9.8.3 Secondary Efficacy Endpoints

Continuous secondary endpoints in the RW phase of the study will be analyzed using a REML–based linear MMRM analysis for the ITT RW population to compare treatment effect between treatment arms at each visit. The MMRM model will include Visit OL22 value (Baseline RW for the respective endpoint) as a covariate; treatment, visit, treatment by visit interaction, and stratification factor as fixed effects; and patients within treatment arms 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. Least-squares means will be used to determine whether there is a difference between treatment arm in terms of the change from Visit OL22 to Visit RW12. SAS statement that implements PROC MIXED will

be used and the sample SAS code is presented in Appendix 3 and can be modified as needed. For select endpoints (i.e. SBP, DBP, $AUC_{glucose}$, HbA1c), missing data at Visit RW12 will be imputed using retrieved dropouts for patients with early treatment discontinuation and using a placebo-based mean imputation for patients that use rescue medication (as defined for each endpoint) before using the MMRM model. As indicated in Section 7.6.2.2.1, if fewer than 10 retrieved dropouts are available, then the main analysis will use a placebo wash-out multiple imputation method instead of the retrieved dropout approach.

For endpoints described as proportions in the RW phase, the point estimate and the two-sided 95% CI will be calculated. Differences in proportions between relacorilant and placebo will be evaluated using a logistic regression model including effects for treatment and the stratification factor (Steingrimsson et al. 2017). Additionally for analyses of patients with DM/IGT, the model will include an effect for the continuous baseline 2-hour oGTT plasma glucose value. The parameter estimates and standard errors, the chi-square test statistics and p-values, along with the odds ratios and 95% CI will be reported. In case of logistic model convergence issues, Fisher's exact test will be used instead. The stratification factor at randomization identifies patients with or without hypertension.

9.8.3.1 Patients with DM/IGT: Loss of Response (AUC-based) in RW Phase

For patients in the DM/IGT subgroup with response at OL22, the proportion of patients with a loss of response with respect to hyperglycemic control (AUC-based) from Visit OL22 to RW12, as compared between relacorilant and placebo arms, where loss of response is defined as a ≥10% increase from baseline in $AUC_{glucose}$ from Visit OL22 to Visit RW12, use of rescue medication (initiation or increase in diabetes medication due to worsening of hyperglycemic control), treatment discontinuation for any reason in RW phase, or patients with missing RW12 $AUC_{glucose}$ values.

The proportion of patients with a loss of response with respect to hyperglycemic control will be calculated for both relacorilant and placebo arms together with corresponding two-sided 95% CI using Clopper-Pearson method for the ITT-RW population. Differences in proportions between relacorilant and placebo will be evaluated using a logistic regression model effects for treatment, the stratification factor (at randomization in IRT), and baseline 2-hour oGTT plasma glucose value (Steingrimsson et al. 2017). The parameter estimates and standard errors, the chi-square test statistics and p-values, along with the odds ratios and 95% CI will be reported. In case of logistic model convergence issues, Fisher's exact test will be used instead. The stratification factor at randomization identifies patients with or without response to hypertension criteria.

A sensitivity analysis will be performed using a logistic regression model where the stratification factor will be based on EDC information.

9.8.3.1.1 Patients with DM/IGT: Loss of Response (AUC-based) in RW Phase Sensitivity Analysis

As a sensitivity analysis for the loss of response (AUC-based), the proportion of patients with loss of response with respect to hyperglycemic control will be examined separately where loss of

response is defined as 1) any increase from baseline in $AUC_{glucose}$ from Visit OL22 to Visit RW12; and 2) as ≥5% increase from baseline in $AUC_{glucose}$ from Visit OL22 to Visit RW12. Use of rescue medication (initiation or increase in diabetes medication due to worsening of hyperglycemic control), treatment discontinuation for any reason in RW phase, or patients with missing RW12 $AUC_{glucose}$ values will also be considered as a loss of response within these 2 sensitivity analyses.

Additionally, each of the three loss of response (AUC-based) definitions (any increase; ≥5% increase; ≥10% increase in $AUC_{glucose}$) will be analyzed separately for DM/IGT patients who had a ≥25% decrease in $AUC_{glucose}$ at OL22 compared to baseline.

9.8.3.2 24-Hour Average Ambulatory Blood Pressure in RW Phase

Mean 24-hour average SBP and DBP will be summarized using descriptive statistics including two-sided 95% CI of the mean by visit, to include the change from baseline by treatment arm for the ITT-RW population. A REML-based linear MMRM will be performed on the ITT-RW population to analyze the change in mean 24-hour average SBP and DBP from Visit OL22 (Baseline RW) to Visit RW12. In this model, missing data at Visit RW12 will be imputed using retrieved dropouts for patients with early treatment discontinuation and using a placebo-based mean imputation for patients that use rescue medication for hypertension.

As indicated in Section 7.6.2.2.1, if fewer than 10 retrieved dropouts are available, then the main analysis will use a placebo wash-out multiple imputation method as described in Section 9.8.3.2.1 instead of the retrieved dropout approach.

The MMRM model will include Visit OL22 value (Baseline RW 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 Randomization to Visit RW12.

A plot of mean 24-hour average SBP and DBP values over time by treatment arm will be presented.

The mean change in the average 24-hour SBP and DBP from Visit OL22 (Baseline RW) to Visit RW12 will be analyzed using an MMRM analysis for the subgroup of hypertension and diastolic hypertension patients in the ITT-RW population. The treatment difference based on 24-hour mean SBP change will also be reported in the subgroup of patients with systolic hypertension at Baseline OL in the ITT-RW population if at least 10 patients in the subgroup are randomized in the RW phase of this study.

Analysis will be performed separately for patients with hypertension at Baseline OL in the ITT-RW population and patients with no hypertension at Baseline OL in the ITT-RW population.

9.8.3.2.1 Placebo Wash-out Multiple Imputation Sensitivity Analysis for 24-Hour Average Ambulatory Blood Pressure

The placebo 'wash-out' analysis means the missing mean 24-hour average SBP and DBP at Visit RW12 data will be imputed by considering a wash-out of the effect of treatment using completers in the placebo arm. Specifically, mean 24-hour average SBP and DBP data for patients on the placebo arm without measurements at Visit RW12 will be imputed using a monotone regression model based on observed mean 24-hour average SBP or DBP data of completers on the placebo arm with intermediate measurements, baseline mean 24-hour average SBP or DBP and stratification factor. For patients on the relacorilant arm with missing Visit RW12 data, the imputation model with only baseline mean 24-hour average SBP or DBP 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 data sets will be generated and an MMRM model with the factors and covariates will be run on each data set and point estimates and standard errors computed and the results 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 RW12 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
- Visit OL22 mean 24-hour average SBP or DBP, a continuous covariate
- Stratification factor (with 2 levels, 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. SAS code example is listed in the Appendix 3.

9.8.3.2.2 Missing At Random (MAR) Sensitivity Analysis for 24-Hour Average Ambulatory Blood Pressure

For the purpose of the secondary analysis, for patients who use rescue medication for hypertension control after randomization and before Visit RW12, the values after first use of rescue medication will not be used in the analysis and will be considered missing at random (MAR). As a supplementary analysis, the change in mean 24-hour average SBP and DBP from Visit OL22 (Baseline RW) to Visit RW12 will be performed using the hypertension subgroup of the ITT-RW population using a linear MMRM model with retrieved dropout data for treatment discontinuation at Visit RW12 and using the embedded MAR assumption for all visits after first

initiating rescue medication for hypertension. The MMRM analysis as described in Section 9.8.3.2 will be performed using the imputed data as described above.

Similarly, for the purpose of the secondary analysis, for patients who discontinue early in the RW phase or use rescue medication for hypertension control after randomization and before Visit RW12, the values after discontinuation or first use of rescue medication will not be used in the analysis and will be considered missing at random (MAR). As a supplementary analysis, the change in mean 24-hour average SBP and DBP from Visit OL22 (Baseline RW) to Visit RW12 will be performed using the hypertension subgroup of the ITT-RW population using a linear MMRM model using the embedded MAR assumption for all visits after treatment discontinuation or first initiating rescue medication for hypertension. The MMRM analysis as described in Section 9.8.3.2 will be performed using the imputed data as described above.

9.8.3.2.3 Tipping Point Supplementary Analysis

The assumption behind the tipping point analysis is to modify the trajectory in patients who drop out from study treatment or use rescue medication for which no observations are available. This pattern of missingness could be represented by a series of progressively more conservative shifts in the mean of missing values in the treatment arm for 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. This technique will be applied to an MMRM model with MAR assumption.

All observed data will be included, regardless of a patient's adherence to treatment or use of prohibited medication. Therefore, we will implement this approach as follows:

- Impute missing values (where patient's data is not measured) for Visit RW12 using regression-based multiple imputations for monotone missingness. 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 Sections 9.8.3.2 will be used to estimate treatment effect on change in SBPfrom Baseline to RW12. 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 SBP. This will complete the generation of missing values at Visit RW12 for this shift value.
- Steps 1-2 will be repeated for at least 5 more shift values to give a total of at least 6 values for one to consider as tipping points. The value of the increment in (δ_{1R}, δ_{1P}) will be set to 2 mmHg for the following comparison pairings (2, 0), (4, 0), (4, 2), (6, 2), and (6, 4).

- The magnitude of the shifts for 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.

9.8.3.3 Body Weight in RW Phase

In patients in the ITT-RW population, body weight will be summarized using descriptive statistics including two-sided 95% CI of the mean by visit, to include the change from baseline by treatment arm. The mean change in body weight from Visit OL22 (Baseline RW) to Visit RW12 will be analyzed using an MMRM model including Visit OL22 (Baseline RW) body weight value as a covariate; treatment, visit, treatment by visit interaction, and stratification factor as fixed effects; and patients within treatment groups as random effects. A REML estimation will be used. An unstructured covariance structure will be used to model within-patient error, and the Kenward-Roger approximation will be used to model denominator degrees of freedom. The analysis for each of the endpoints will determine whether there is a difference between treatment groups in terms of change from Randomization to Visit RW12.

A plot of mean body weight values over time by treatment arm will be presented.

9.8.3.4 $AUC_{glucose}$ for Patients with Response to DM/IGT Criteria in RW Phase

$AUC_{glucose}$ will be calculated based on results of the plasma 2-hour oGTT test taken at Baseline OL, OL6, OL10, OL14, OL18, OL22, RW4, RW8 and RW12. 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 7.6.2.2.2 describes handling missing data for calculation of $AUC_{glucose}$.

The analysis for the change in $AUC_{glucose}$ from Visit OL22 (Baseline RW) to Visit RW12 will be performed using a linear MMRM model with retrieved dropout data for treatment discontinuation and using a placebo-based mean imputation at Visit RW12 for patients that use rescue medication using the DM/IGT subgroup of the ITT-RW population. The MMRM model will include the following fixed effects:

- Treatment (with 2 levels, relacorilant and placebo)
- Visit (Scheduled), a categorical factor
- Treatment-by-visit interaction
- Visit OL22 $AUC_{glucose,}$ a continuous covariate
- Stratification factor (with 2 levels, with or without hypertension)

The MMRM model will include patients within treatment arms as random effects. REML estimation will be used. An unstructured covariance structure 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.

As indicated in Section 7.6.2.2.2, if fewer than 10 retrieved dropouts are available, then the main analysis will use a placebo wash-out multiple imputation method as described in Section 9.8.3.4.1 instead of the retrieved dropout approach.

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

Estimated least squares means (± SE) and 95% CIs for change in $AUC_{glucose}$ will be plotted by treatment and over time (from Visit OL22 and all visits up to Visit RW12).

SAS statement that implements PROC MIXED will be used and the sample SAS code is presented in Appendix 3 and can be modified as needed.

9.8.3.4.1 Placebo Wash-out Multiple Imputation Sensitivity Analysis for $AUC_{glucose}$

If enough patient data are collected to use a retrieved dropout imputation (10 or more retrieved dropouts) for the secondary analysis, then the following supplementary analysis will be performed for $AUC_{glucose}$ (Section 7.6.2.2.2)

In this study, the treatment effect is determined by loss of response with regards to response to DM/IGT criteria. The placebo 'wash-out' analysis means the missing $AUC_{glucose}$ at Visit RW12 data will be imputed by considering a wash-out of the effect of treatment using completers in the placebo arm. Specifically, $AUC_{glucose}$ data for patients on the placebo arm without measurements at Visit RW12 will be imputed using a monotone regression model based on observed $AUC_{glucose}$ data of completers on the placebo arm with intermediate measurements, baseline $AUC_{glucose}$ and stratification factor. For patients on the relacorilant arm with missing Visit RW12 data, the imputation model with only baseline $AUC_{glucose}$ 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 data sets will be generated and an MMRM model with the factors and covariates will be run on each data set and point estimates and standard errors computed and the results 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 RW12 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
- Visit OL22 $AUC_{glucose}$, a continuous covariate
- Stratification factor (with 2 levels, with or without hypertension)

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. SAS code example is listed in the Appendix 3.

9.8.3.4.2 Missing at Random (MAR) Imputation Sensitivity Analysis for $AUC_{glucose}$

For patients who use rescue medication for hyperglycemia control after randomization and before Visit RW12, the values collected after rescue medication is first used are irrelevant to the clinical question of interest, and thus will not be used in the analysis, and will be considered missing at random (MAR). As a supplementary analysis, the change in $AUC_{glucose}$ from Visit OL22 (Baseline RW) to Visit RW12 will be performed using the DM/IGT subgroup of the ITT-RW population using a linear MMRM model with retrieved dropout data for treatment discontinuation at Visit RW12 and the embedded MAR assumption for all visits after first use of rescue medication for patients that use rescue medication for hyperglycemia control. The MMRM analysis as described in Section 9.8.3.4 will be performed using the imputed data as described above.

Similarly, for patients for patients who discontinue early in the RW phase or use rescue medication for hyperglycemia control after randomization and before Visit RW12, the values after discontinuation or first use of rescue medication will be considered missing at random (MAR). As a supplementary analysis, the change in $AUC_{glucose}$ from Visit OL22 (Baseline RW) to Visit RW12 will be performed using the DM/IGT subgroup of the ITT-RW population using a linear MMRM model using the embedded MAR assumption for all visits after discontinuation or first use of rescue medication for patients that use rescue medication for hyperglycemia control. The MMRM analysis as described in Section 9.8.3.4 will be performed using the imputed data as described above.

9.8.3.4.3 Tipping Point Supplementary Analysis

A similar approach to the tipping point described in Section 9.8.3.2.2, will be implemented for $AUC_{glucose}$ with the increment in (δ_{1R}, δ_{1P}) set to 1 hr*mmol/L for the following comparison pairings (1, 0), (2, 0), (3, 0), (2, 1), (3, 1), and (3, 2).

9.8.3.5 Patients with DM/IGT: Comprehensive Loss of Response in RW Phase

For patients in the DM/IGT subgroup in the ITT-RW population with response at OL22, the proportion of patients with a comprehensive loss of response with respect to hyperglycemic control from Visit OL22 (Baseline RW) to Visit RW12 will be calculated based on the plasma 2-

hour oGTT test to compare relacorilant and placebo, where comprehensive loss of response is defined as follows:

In patients with DM:

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

OR

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

OR

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

In patients with IGT:

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

OR

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

The proportion of patients with a comprehensive loss of response with respect to hyperglycemic control will be calculated for both relacorilant and placebo arms together with corresponding two-sided 95% CI using Clopper-Pearson method for the ITT-RW population separately for both definitions. Differences in proportions between relacorilant and placebo will be evaluated using a logistic regression model effects for treatment, the stratification factor, and baseline 2-hour oGTT plasma glucose value (Steingrimsson et al. 2017). The parameter estimates and standard errors, the chi-square test statistics and p-values, along with the odds ratios and 95% CI will be reported. In case of logistic model convergence issues, Fisher's exact test will be used instead. The stratification factor at randomization identifies patients with or without hypertension.

9.8.3.6 HbA1c in RW Phase

The analysis for the change in HbA1c from Visit OL22 (Baseline RW) to Visit RW12 will be performed using a linear MMRM model with retrieved dropout data for treatment discontinuation and using a placebo-based mean imputation at Visit RW12 for patients that use rescue medication using the DM/IGT subgroup of the ITT-RW population.

As indicated in Section 9.8.3 if fewer than 10 retrieved dropouts are available, then placebo wash-out multiple imputation method will be used instead of the retrieved dropout approach.

The placebo 'wash-out' analysis means the missing HbA1c at Visit RW12 data will be imputed by considering a wash-out of the effect of treatment using completers in the placebo arm.

Specifically, HbA1c data for patients on the placebo arm without measurements at Visit RW12 will be imputed using a monotone regression model based on observed HbA1c data of completers on the placebo arm with intermediate measurements, baseline HbA1c and stratification factor. For patients on the relacorilant arm with missing Visit RW12 data, the imputation model with only baseline HbA1c 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 data sets will be generated and an MMRM model with the factors and covariates will be run on each data set and point estimates and standard errors computed and the results 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 RW (Visit OL22) to Visit RW12 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
- Visit OL22 HbA1c, a continuous covariate
- Stratification factor (with 2 levels, with or without hypertension)

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. SAS code example is listed in the Appendix 3.

9.8.4 Exploratory Efficacy Endpoints

9.8.4.1 Analysis of the Exploratory Efficacy Endpoints in the RW Phase

Continuous exploratory endpoints in the RW phase of the study will be analyzed using a REML–based linear MMRM analysis for the ITT-RW population to compare treatment effect between treatment arms at each visit. The MMRM model will include Visit OL22 value (Baseline RW for the respective endpoint) as a covariate; treatment, visit, treatment by visit interaction, and stratification factor as fixed effects; and patients within treatment arms 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. Least-squares means will be used to determine whether there is a difference between treatment arm in terms of the change from Visit OL22 to Visit RW12. SAS statement that implements PROC MIXED will be used and the sample SAS code is presented in Appendix 3 and can be modified as needed.

For endpoints described as proportions in the RW phase, the point estimate and the two-sided 95% CI will be calculated. Differences in proportions between relacorilant and placebo will be evaluated using a logistic regression model including effects for treatment and the stratification factor (Steingrimsson et al. 2017). Additionally for analyses of patients with DM/IGT, the model will include an effect for the continuous baseline 2-hour oGTT plasma glucose value. The parameter estimates and standard errors, the chi-square test statistics and p-values, along with the odds ratios and 95% CI will be reported. In case of logistic model convergence issues, Fisher's exact test will be used instead. The stratification factor at randomization identifies patients with or without hypertension and/or with or without DM/IGT.

9.8.4.1.1 24-Hour Average HR in RW Phase

Mean 24-hour average HR (based on ABPM) will be summarized using descriptive statistics including two-sided 95% CI of the mean by visit, to include the change from baseline by treatment arm for the ITT-RW population. A REML-based linear MMRM will be performed on the ITT-RW population to analyze the change in mean 24-hour average HR from Visit OL22 (Baseline RW) to Visit RW12. The MMRM model will include Visit OL22 mean 24-hour average HR value 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 Randomization to Visit RW12.

A plot of mean 24-hour average HR values over time by treatment arm will be presented.

Analysis will be performed separately for patients with hypertension at Baseline OL in the ITT-RW population and patients with no hypertension at Baseline OL in the ITT-RW population.

9.8.4.1.2 Daytime and Nighttime Average SBP, DBP, and HR in RW Phase

Daytime and Nighttime average SBP, DBP, and HR at Visit RW12 will be analyzed using a REML-based linear MMRM model. The MMRM model will include Visit OL22 value (Baseline RW 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 Randomization to Visit RW12.

Two sets of Daytime and Nighttime windows will be applied:

- Daytime (defined as 06:00 to 21:59) and Nighttime (defined as 22:00 to 05:59)
- Daytime (defined as 09:00 to 21:00) and Nighttime (defined as 01:00 to 06:00)

Analysis will be performed separately for patients with hypertension at Baseline OL in the ITT-RW population and patients with no hypertension at Baseline OL in the ITT-RW population.

A plot of mean 24-hour average daytime and nighttime values over time by treatment arm will be presented.

9.8.4.1.3 Body-fat Composition by DXA in RW Phase

In patients in the ITT-RW population, changes in the percent and absolute amounts of total mass, lean mass and fat mass as measured by DXA scan will be summarized using descriptive statistics including two-sided 95% CI of the mean by visit, to include the change from baseline by treatment arm. Total mass, lean mass, and fat mass will also be analyzed by a Wilcoxon signed-rank test to evaluate if there is a significant change from Visit OL22 (Baseline RW) to each visit up to Visit RW12 for each treatment arm.

9.8.4.1.4 Cushing QoL in RW Phase

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:

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

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 5). The subscales of the Cushing QoL are standardized with the following formula:

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

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.

Table 5 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

Among patients in the ITT-RW population, standardized Cushing QoL total score, physical problems subscale, and psychosocial issues subscale will be summarized using descriptive statistics including two-sided 95% CI of the mean by visit, to include the change from baseline by treatment arm. The mean change in Cushing QoL total score, physical problems subscale, and psychosocial issues subscale will be analyzed using a REML-based linear MMRM model. The MMRM model will include Visit OL22 (Baseline RW) standardized Cushing QoL total score value 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 Randomization to Visit RW12.

Where appropriate, Cushing QoL assessments will also be analyzed by a Wilcoxon signed-rank test to evaluate if there is a significant change from Visit OL22 (Baseline RW) to Visit RW12 for each treatment arm.

A plot of the mean standardized Cushing QoL total score, physical problems subscale, and psychosocial issues subscale over time by treatment arm will be presented.

9.8.4.1.5 HbA1c in RW Phase

HbA1c will be summarized using descriptive statistics including two-sided 95% CI of the mean by visit, to include the change from baseline by treatment arm for the ITT-RW population. The mean change in HbA1c from Visit OL22 (Baseline RW) to Visit RW12 will be analyzed using an MMRM analysis for patients in the DM/IGT subgroup of the ITT-RW population with HbA1c ≥6.5% at Baseline OL. The MMRM model will include Visit OL22 (Baseline RW)

HbA1c value as a covariate; treatment, visit, treatment by visit interaction, and stratification factor as fixed effects; and patients within treatment groups as random effects. A REML estimation will be used. An unstructured covariance structure will be used to model within-patient error, and the Kenward-Roger approximation will be used to model denominator degrees of freedom. The analysis for each of the endpoints will determine whether there is a difference between treatment groups in terms of change from Randomization to Visit RW12.

A plot of mean HbA1c values over time by treatment arm will be presented.

The analysis will be performed separately for patients with DM at Baseline OL in the ITT-RW population, and patients with IGT at Baseline OL in the ITT-RW population.

9.8.4.1.6 Change in $AUC_{glucose}$

$AUC_{glucose}$ for all patients (DM/IGT and hypertension) in the ITT-RW population that have plasma 2-hour oGTT test values will be summarized using descriptive statistics including two-sided 95% CI of the mean by visit, to include the change from baseline by treatment arm. The mean change in $AUC_{glucose}$ from Visit OL22 (Baseline RW) to Visit RW12 will be analyzed for patients in the ITT-RW population using an MMRM model including Visit OL22 (Baseline RW) $AUC_{glucose}$ value as a covariate; treatment, visit, treatment by visit interaction, and stratification factor as fixed effects; and patients within treatment groups as random effects. A REML estimation will be used. An unstructured covariance structure will be used to model within-patient error, and the Kenward-Roger approximation will be used to model denominator degrees of freedom. The analysis for each of the endpoints will determine whether there is a difference between treatment groups in terms of change from Randomization to Visit RW12.

A plot of mean $AUC_{glucose}$ values over time by treatment arm will be presented for the ITT-RW population.

Additionally, the change in $AUC_{glucose}$ from Visit OL22 (Baseline RW) to Visit RW12 will be analyzed for DM/IGT patients in the ITT-RW population excluding those who received long-acting insulin.

9.8.4.1.7 oGTT Plasma Glucose in RW Phase

Plasma glucose (mmol/L) from the 2-hour oGTT test will be summarized using descriptive statistics including two-sided 95% CI of the mean by visit and time point (pre-glucose drink and 0.5, 1, 1.5, and 2 hours post glucose drink), to include the change from Visit OL22 to Visit RW12 by treatment arm for the ITT-RW population. For patients in the DM/IGT subgroup in the ITT-RW population, the mean change in plasma glucose at each timepoint from Visit OL22 (Baseline RW) to Visit RW12 will be analyzed using an MMRM model including Visit OL22 value (Baseline RW for the respective timepoint) as a covariate; treatment, visit, treatment by visit interaction, and stratification factor as fixed effects; and patients within treatment groups as random effects. A REML estimation will be used. An unstructured covariance structure will be used to model within-patient error, and the Kenward-Roger approximation will be used to model denominator degrees of freedom. The analysis for each of the endpoints will determine whether there is a difference between treatment groups in terms of change from Randomization to Visit

RW12 at each time point (pre-glucose drink and 0.5, 1, 1.5, and 2 hours post glucose drink) for each treatment arm. A column summarizing change from pre-glucose drink values will also be included.

A plot of mean plasma glucose (mmol/L) values over time by treatment arm will be presented.

The analysis will be performed separately for the subgroup of patients with DM at Baseline OL in the ITT-RW population, patients with IGT at Baseline OL in the ITT-RW population.

9.8.4.1.8 Analysis of Other Continuous Exploratory Efficacy Endpoints in RW Phase

The continuous exploratory efficacy endpoints include waist circumference; serum osteocalcin; sit-to-stand test score; trail-making test score; sex-hormone levels (estradiol, total and free testosterone, sex-hormone–binding globulin, follicle-stimulating hormone, and luteinizing hormone) separately for male and female patients; urinary free cortisol (UFC), late-night salivary cortisol and plasma adrenocorticotropic hormone (ACTH); and daytime and nighttime average blood pressure.

In all patients in the ITT-RW population, all continuous exploratory efficacy endpoints will be summarized using descriptive statistics including two-sided 95% CI of the mean by visit, to include the change from Visit OL22 to Visit RW12 by treatment arm. These efficacy assessments will also be analyzed by a Wilcoxon signed-rank test to evaluate if there is a significant change from Visit OL22 to Visit RW12 for each treatment arm. Fasting serum cortisol, UFC, late-night salivary cortisol, osteocalcin, and plasma ACTH levels will be presented separately for patients with ACTH independent and ACTH dependent Cushing syndrome.

Continuous exploratory efficacy endpoints in the RW phase of the study will be analyzed using a similar approach as described in Section 9.8.3. A REML–based linear MMRM analysis will be used. The MMRM model will include Visit OL22 value (for the respective endpoint) as a covariate; treatment, visit, treatment by visit interaction, and stratification factor as fixed effects; and patients within treatment arms 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. Least-squares means will be used to estimate the change from Visit OL22 to Visit RW12.

A plot of the mean UFC and ACTH values over time by treatment arm will be presented separately for patients with ACTH independent and ACTH dependent Cushing syndrome.

9.8.4.1.9 ACTH in Patients with Adrenal Cushing Syndrome (ACTH Independent) in RW Phase

In all patients with adrenal Cushing syndrome (ACTH independent) in the ITT-RW population, ACTH will be summarized using descriptive statistics including two-sided 95% CI of the mean by visit, to include the change from Visit OL22 to Visit RW12 by treatment arm. ACTH will also be analyzed by a Wilcoxon signed-rank test to evaluate if there is a significant change from Visit OL22 to Visit RW12 for each treatment arm.

A plot of mean ACTH values over time by treatment arm will be presented.

In patients with adrenal Cushing syndrome (ACTH independent) in the ITT-RW population, the ACTH in the RW phase of the study will be analyzed using a similar approach as described above in Section 9.8.3. A REML–based linear MMRM analysis will be used. The MMRM model will include Visit OL22 value (for the respective endpoint) as a covariate; treatment, visit, treatment by visit interaction, and stratification factor as fixed effects; and patients within treatment arms 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. Least-squares means will be used to estimate the change from Visit OL22 to Visit RW12.

9.8.4.1.10 Antidiabetic Medication and Antihypertensive Medication in RW Phase

In patients with uncontrolled hypertension at Baseline OL, the number and proportion of patients whose dose of antihypertensive medication decreased, discontinued, stayed the same, or increased from Visit OL22 (Baseline RW) to Visit RW12 will be summarized, among those patients taking such medications at Baseline RW. Antihypertensive medications include potassium sparing diuretics.

In patients with DM/IGT at Baseline OL, the number and proportion of patients whose dose of diabetes medication decreased, discontinued, stayed the same, or increased from Visit OL22 (Baseline RW) to Visit RW12 will be summarized, among those patients taking such medications at Baseline RW. Diabetes and antihypertensive medication will be summarized using the ITT-RW population. 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. The stratification factor at randomization identifies patients with or without hypertension.

9.8.4.1.11 Global Clinical Response Score in RW Phase

In all patients, the DRB (Data Review Board) will evaluate Global Clinical Response (Katznelson et al. 2014). Each of 3 members of the DRB will review the 7 categories of clinical parameters evaluate whether a patient's signs and symptoms of Cushing syndrome have changed and will rate the patient's overall response based on the totality of signs and symptoms as +1 (improved), 0 (unchanged), or −1 (worsened) at every visit after Baseline OL. Each patient's final score will be the median of the 3 ratings. The change from Visit OL22 (Baseline RW) to Visit RW12 will be summarized using a frequency table including proportions of patients that worsened (with overall response category −1 (worsened)) and patients that did not worsen (with overall response categories of +1 [improved] or 0 [unchanged]) by visit and by treatment arm for the ITT-RW population. Confidence intervals (95% exact binomial two-sided CI using Clopper-Pearson method) will also 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. The stratification factor at randomization identifies patients with or without hypertension.

9.8.4.1.12 Response Analysis ($AUC_{glucose}$) from Baseline OL to Visit RW12 in Patients with DM

For patients in the DM subgroup in the ITT-RW population, the proportion of patients who achieve 25% reduction in $AUC_{glucose}$ from Baseline OL to Visit RW12 will be analyzed. The number and percentage of patients who are responders will be presented along with a 95% exact binomial two-sided CI (Clopper-Pearson). 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. The stratification factor at randomization identifies patients with or without hypertension.

For the purposes of this responder analysis, patients who, during the RW phase, initiate rescue medications, discontinue treatment or do not meet a 25% reduction in $AUC_{glucose,}$ at Visit RW12 will be considered non-responders. If there are at least 10 patients in the subgroup of patients with DM/IGT, but without hypertension at Baseline OL, that continue in the RW phase, then this endpoint will also be analyzed in this particular subgroup of patients.

9.8.4.1.13 Analysis of the Exploratory Efficacy Endpoints from Baseline OL to Visit RW12

For patients in the ITT-RW population, the mean change from Baseline OL to Visit RW12 will be compared between relacorilant and placebo in the following:

- sex-hormone levels (estradiol, total and free testosterone, sex-hormone–binding globulin, follicle-stimulating hormone, and luteinizing hormone) separately for male and female patients.
- ACTH in all patients, and separately for patients with adrenal Cushing syndrome (ACTH independent) and ACTH dependent Cushing syndrome.
- $AUC_{glucose}$, $AUC_{insulin}$, Matsuda Index, and HOMA-IR in all patients and separately in patients with DM/IGT only.
- 24hr, daytime, and nighttime average blood pressure in all patients, and separately in patients with uncontrolled hypertension with or without DM/IGT.

Continuous exploratory efficacy endpoints in the RW phase of the study will be analyzed using a similar approach as described in Section 9.8.3. A REML–based linear MMRM analysis will be used. The MMRM model will include Baseline OL value (for the respective endpoint) as a covariate; treatment, visit, treatment by visit interaction, and stratification factor as fixed effects; and patients within treatment arms 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. Least-squares means will be used to estimate the change from Baseline OL to Visit RW12.

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:

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

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.).

$AUC_{insulin}$ will be derived similar to $AUC_{glucose}$ (Section 9.8.3.4).

9.8.4.1.14 Subgroup Analysis for Patients with Response to DM/IGT and Hypertension

In the subgroup of patients who were randomized based on improvement of both DM/IGT and hypertension, the following analyses will be performed for the RW phase:

Loss of Response with Respect to Hypertension:

For patients in the DM/IGT and hypertension subgroup in the ITT-RW population with response to both comorbidities at OL22, the proportion of patients with a loss of response with respect to hypertension control (defined in Section 9.8.2.1) from Visit OL22 (Baseline RW) to Visit RW12 will be calculated. The proportion of patients with a loss of response with respect to hypertension control will be calculated for both relacorilant and placebo arms together with corresponding two-sided 95% CI using Clopper-Pearson method for the DM/IGT and hypertension subgroup of the ITT-RW population. The analysis as described in Section 9.8.2.2 will be performed for patients in the DM/IGT and hypertension subgroup of the ITT-RW population.

Loss of Response with Respect to Hyperglycemic Control (AUC-based):

For patients in the DM/IGT and hypertension subgroup in the ITT-RW population with response to both comorbidities at OL22, the proportion of patients with a loss of response with respect to hyperglycemic control (AUC-based, defined in Section 9.8.3.1) from Visit OL22 (Baseline RW) to Visit RW12 will be calculated. The proportion of patients with a loss of response with respect to hyperglycemic control will be calculated for both relacorilant and placebo arms together with corresponding two-sided 95% CI using Clopper-Pearson method for the DM/IGT and hypertension subgroup of the ITT-RW population. The analysis as described in Section 9.8.3.1 will be performed for patients in the DM/IGT and hypertension subgroup of the ITT-RW population.

9.8.4.1.15 Loss of Response to Hypertension or Hyperglycemia in RW Phase

In all patients randomized in the RW phase, proportion of patients with a loss of response with respect to hypertension or hyperglycemia from Visit OL22 to Visit RW12 based on 24-hour ABPM and $AUC_{glucose}$ as compared between relacorilant and placebo arms, where loss of response is defined as follows:

- In patients with hypertension only at Baseline OL

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

The proportion of patients with a loss of response with respect to hypertension or hyperglycemia will be calculated for both relacorilant and placebo arms together with corresponding two-sided 95% CI using Clopper-Pearson method for the ITT-RW population. Differences in proportions between relacorilant and placebo will be evaluated using a logistic regression model effects for treatment and the stratification factor (at Baseline OL) (Steingrimsson et al. 2017). The parameter estimates and standard errors, the chi-square test statistics and p-values, along with the odds ratios and 95% CI will be reported. In case of logistic model convergence issues, Fisher's exact test will be used instead.

9.8.4.2 Analysis of the Exploratory Efficacy Endpoints in the OL Phase

Continuous exploratory endpoints in the OL phase of the study will be analyzed using a restricted maximum-likelihood (REML)–based linear MMRM analysis for the mITT OL population. 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. 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 OL22. The analysis using MMRM will be main result. In addition, the Wilcoxon signed-rank test 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. SAS statement that implements PROC MIXED will be used and the sample SAS code is presented in Appendix 3 and can be modified as needed.

For all endpoints in the OL phase that are described as proportions, the point estimate and the two-sided 95% CI will be calculated.

9.8.4.2.1 24-Hour Ambulatory Blood Pressure in OL Phase

24-hour systolic and diastolic ambulatory blood pressure will be obtained by the patient at home using an ambulatory BP monitor. The mean change in the mean 24-hour SBP and DBP from Baseline OL to OL22 will be analyzed using an MMRM analysis for the subgroup of systolic hypertension and diastolic hypertension patients in the mITT-OL population. A REML–based linear MMRM analysis will be used. 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. 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 OL22.

Mean 24-hour SBP and DBP, will be summarized using descriptive statistics including two-sided 95% CI of the mean by visit, to include the change from baseline for the mITT-OL population. Mean 24-hour SBP and DBP will also be analyzed by a Wilcoxon signed-rank test to evaluate if there is a significant change from Baseline OL by visit up to Visit OL22/ET for the mITT-OL population.

The protocol has been amended to collect ABPM assessments at Visit OL2. Since this was added only in protocol Amendment 4 (17 December 2020), there may be a sizable number of patients with missing values. A sensitivity analysis for the mITT-OL population will be conducted using the method defined in Section 9.8.3 with one model that includes OL2 and one without OL2 to evaluate if there is any difference.

A plot of mean 24-hour SBP and DBP values over time will be presented.

Analysis will be performed separately for patients with uncontrolled hypertension at Baseline OL in the mITT-OL population, patients without uncontrolled hypertension (i.e. patients with only DM/IGT) at Baseline OL in the mITT-OL population, patients with uncontrolled hypertension at Baseline OL in the mITT-OL population and treated with antihypertensive medications, patients with uncontrolled hypertension at Baseline OL in the mITT-OL population and not treated with antihypertensive medications, patients with controlled hypertension at Baseline OL in the mITT-OL population and treated with antihypertensive medications, patients without uncontrolled hypertension at Baseline OL in the mITT-OL population and not treated with antihypertensive medications.

9.8.4.2.2 Cushing QoL in OL Phase

The mean change in the standardized Cushing QoL total score, physical problems subscale, and psychosocial issues subscale (Section 9.8.4.1.4) from Baseline OL to OL22 will be analyzed using a 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. 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 OL22.

In all patients in the mITT-OL population, Cushing QoL will be summarized using descriptive statistics including two-sided 95% CI of the mean by visit, to include the change from baseline. Cushing QoL assessments will also be analyzed by a Wilcoxon signed-rank test to evaluate if there is a significant change compared with Baseline OL by visit up to Visit OL22/ET.

A plot of the mean standardized Cushing QoL total score, physical problems subscale, and psychosocial issues subscale over time will be presented.

In addition, the null hypothesis that the mean change from baseline in the Cushing QoL total score (original scale) is less or equal to 10 points (versus the alternative hypothesis that it is >10 points) will be rejected if the lower bound of the two-sided 95% CI (or, equivalently, 1-sided 97.5% CI) exceeds 10. The change of 10 points in Cushing's QoL is considered clinically meaningful.

9.8.4.2.3 Body-fat Composition by DXA in OL Phase

In all patients in the mITT-OL population, changes in the percent and absolute amounts of total mass, lean mass and fat mass as measured by DXA scan will be summarized using descriptive statistics including two-sided 95% CI of the mean by visit, to include the change from baseline. A REML–based linear MMRM analysis will be used to evaluate the change in each parameter from Baseline OL to OL22. 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. 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 OL22.

The absolute amounts of total mass, lean mass and fat mass will also be analyzed by a Wilcoxon signed-rank test to evaluate if there is a significant change compared with Baseline OL at each visit up to Visit OL22/ET.

9.8.4.2.4 Beck Depression Inventory®-II (BDI-II) in OL Phase

In all patients in the mITT-OL population, the total BDI-II score, which is based on a 21-question self-report inventory that measures depression (Beck et al. 1996), will be summarized using descriptive statistics including two-sided 95% CI of the mean by visit, to include the change from baseline. A REML–based linear MMRM analysis will be used. 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. 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 OL22.

The total BDI-II score will also be analyzed by a Wilcoxon signed-rank test to evaluate if there is a significant change compared with Baseline OL at each visit up to Visit OL22/ET for the mITT-OL population.

9.8.4.2.5 Body Weight in OL Phase

The mean change in body weight from Baseline OL to OL22 will be analyzed using a REML–based linear MMRM analysis for the mITT-OL population. 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. 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 OL22.

In all patients in the mITT-OL population, body weight will be summarized using descriptive statistics including two-sided 95% CI of the mean by visit, to include the change from baseline. Body weight will also be analyzed by a Wilcoxon signed-rank test to evaluate if there is a significant change compared with Baseline OL at each visit up to Visit OL22/ET.

A plot of mean body weight values over time will be presented.

9.8.4.2.6 oGTT Plasma Glucose in OL Phase

Plasma glucose (mmol/L) from the 2-hour oGTT test will be summarized using descriptive statistics including two-sided 95% CI of the mean by visit and time point (pre-glucose drink and 0.5, 1, 1.5, and 2 hours post glucose drink), to include the change from baseline for the mITT-OL population. A REML-based linear MMRM will be used to analyze the mean change in the plasma glucose from Baseline OL to Visit OL22 for the mITT-OL population. 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. 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 OL22.

In addition, plasma glucose (mmol/L) will also be analyzed by a Wilcoxon signed-rank test to evaluate if there is a significant change compared with Baseline OL at each time point (pre-glucose drink and 0.5, 1, 1.5, and 2 hours post glucose drink) for the change from baseline by visit up to Visit OL22/ET. A column summarizing change from pre-glucose drink values will also be included.

A plot of mean plasma glucose (mmol/L) values over time will be presented.

Analysis will be performed separately for the subgroup of patients with DM at Baseline OL in the mITT-OL population, patients with IGT at Baseline OL in the mITT-OL population, and patients with normal blood glucose at Screening in the mITT-OL population.

9.8.4.2.7 HbA1c in OL Phase

REML-based MMRM analysis will be performed on the mITT-OL population to analyze the change in HbA1c from Baseline OL to Visit OL22. 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. 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 OL22.

HbA1c will be summarized using descriptive statistics including two-sided 95% CI of the mean by visit, to include the change from baseline. HbA1c will be analyzed by a Wilcoxon signed-rank test to evaluate if there is a significant change compared with Baseline OL at each visit up to Visit OL22/ET for the mITT-OL population.

A plot of mean HbA1c values over time will be presented.

Analysis will be performed separately for patients with DM at Baseline OL in the mITT-OL population, patients with DM at Baseline OL in the mITT-OL population with HbA1c ≥6.5% at Baseline OL, patients with IGT at Baseline OL in the mITT-OL population, and patients with normal blood glucose at Screening in the mITT-OL population.

9.8.4.2.8 Change in $AUC_{glucose}$ from Baseline to Visit OL22 in Patients with DM/IGT

The change in $AUC_{glucose}$ from Baseline OL to Visit OL22 will also be analyzed using a REML-based linear MMRM for the mITT-OL population. 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. 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 OL22.

Additionally, $AUC_{glucose}$ will be summarized using descriptive statistics including two-sided 95% CI of the mean, and the change in $AUC_{glucose}$ from Baseline OL up to Visit OL22/ET will be analyzed by a Wilcoxon signed-rank test to evaluate if there is a significant change compared with Baseline OL at each visit for the mITT-OL population.

The analysis will be performed separately for patients with DM at Baseline OL in the mITT-OL population, patients with IGT at Baseline OL in the mITT-OL population, and patients with normal blood glucose at Screening in the mITT-OL population.

9.8.4.2.9 Analysis of Other Continuous Exploratory Efficacy Endpoints in OL Phase

The continuous exploratory efficacy endpoints include waist circumference; serum osteocalcin; sit-to-stand test score; trail-making test score; sex-hormone levels (estradiol, total and free testosterone, sex-hormone–binding globulin, follicle-stimulating hormone, and luteinizing hormone) separately for male and female patients; urinary free cortisol (UFC), late-night salivary cortisol and plasma adrenocorticotropic hormone (ACTH); and daytime and nighttime average blood pressure.

In patients in the mITT-OL population, all continuous exploratory efficacy endpoints will be summarized using descriptive statistics including two-sided 95% CI of the mean by visit, to include the change from baseline. Fasting serum cortisol, UFC, late-night salivary cortisol, osteocalcin, and plasma ACTH levels will be presented separately for patients with ACTH independent and ACTH dependent Cushing syndrome.

Continuous exploratory efficacy endpoints in the OL phase of the study may be analyzed using a similar approach as described above in Section 9.8.4. A REML–based linear MMRM analysis will be used. The MMRM model will use visit as a fixed effect, and patient as a random effect.

An unstructured covariance structure will be used to model the within-patient errors. 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 OL22.

A plot of the mean UFC and ACTH values over time will be presented separately for patients with ACTH independent and ACTH dependent Cushing syndrome. Additionally, A plot of mean 24-hour average daytime and nighttime values over time will be presented.

9.8.4.2.10 ACTH in Patients with Adrenal Cushing Syndrome (ACTH Independent) in OL Phase

In all patients with adrenal Cushing syndrome (ACTH independent) in the mITT-OL population, ACTH will be summarized using descriptive statistics including two-sided 95% CI of the mean by visit, to include the change from baseline. A REML–based linear MMRM analysis will be used. 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. 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 OL22. ACTH will also be analyzed by a Wilcoxon signed-rank test to evaluate if there is a significant change compared with baseline at Visit OL22/ET.

A plot of mean ACTH values over time will be presented.

In patient with Adrenal Cushing syndrome (ACTH independent), the ACTH in OL phase of the study will be analyzed using a similar approach as described above in Section 9.8.4. A REML–based linear MMRM analysis will be used. The MMRM model will use visit as a fixed effect, and patient as a random effect. An unstructured covariance structure will be used to model the within-patient errors. 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 OL22.

9.8.4.2.11 Responder Analysis in OL Phase in Patients with Hypertension

In patients with uncontrolled hypertension at Baseline OL in the mITT-OL population, mean 24-hour SBP and DBP per patient per visit will be included in the analysis. A responder will be defined as a patient who experiences at least a 5 mm Hg decrease in mean DBP or SBP from Baseline OL to Visit OL22, without worsening of either (defined as increase in mean SBP or DBP by at least 5 mm Hg). The number and percentage of patients who are responders will be presented along with a 95% exact binomial two-sided CI (Clopper-Pearson).

9.8.4.2.12 Antidiabetic Medication and Antihypertensive Medication in OL Phase

In patients with uncontrolled hypertension at Baseline OL in the mITT-OL population, the number and proportion of patients whose dose of antihypertensive medication decreased, discontinued, stayed the same, or increased from Baseline OL to Visit OL22 will be summarized, among those patients taking such medications at Baseline OL. In patients with DM/IGT at

Baseline OL in the mITT-OL population, the number and proportion of patients whose dose of diabetes medication decreased, discontinued, stayed the same, or increased from Baseline OL to Visit OL22 will be summarized, among those patients taking such medications at Baseline OL. Separately, in patients with DM at Baseline OL in the mITT-OL population with HbA1c ≥6.5% at Baseline OL, the number and proportion of patients whose dose of diabetes medication decreased, discontinued, stayed the same, or increased from Baseline OL to Visit OL22 will be summarized, among those patients taking such medications at Baseline OL.

9.8.4.2.13 Global Clinical Response Score in OL Phase

In all patients, the DRB (Data Review Board) will evaluate Global Clinical Response (Katznelson et al. 2014) at each visit. Each of 3 members of the DRB will review the 7 categories of clinical parameters evaluate whether a patient's signs and symptoms of Cushing syndrome have changed and will rate the patient's overall response based on the totality of signs and symptoms as +1 (improved), 0 (unchanged), or −1 (worsened) at every visit after Baseline OL. Each patient's final score will be the median of the 3 ratings. The change from baseline to Visit OL22 will be summarized using frequency table including proportions of patients that improve (with overall response category +1 (improved)) and patients that did not improve (with overall response categories 0 [unchanged], or −1 [worsened]) by visit for the mITT-OL population. Confidence intervals (95% exact binomial two-sided CI using Clopper-Pearson method) will also be presented.

9.8.4.2.14 Responder Analysis in OL Phase in Patients with DM/IGT

In patients with DM at Baseline OL in the mITT-OL population, HbA1c, 2-hour plasma oGTT glucose and total daily insulin dose per patient per visit will be included in the analysis. A responder will be defined as a patient who experiences at least 0.5% decrease in HbA1c from Baseline OL to Visit OL22, or 2-hour plasma oGTT glucose is normalized (<140 mg/dL) or decreased at least 50 mg/dL from Baseline OL to Visit OL22 or total daily insulin dose has decreased by at least 25% with HbA1c unchanged or decreased compared with Baseline OL. In patients with IGT at Baseline OL in the mITT-OL population, 2-hour plasma oGTT glucose per patient per visit will be included in the analysis. A responder will be defined as a patient whose 2-hour plasma oGTT glucose is normalized (<140 mg/dL) from Baseline OL to Visit OL22. The number and percentage of patients who are responders will be presented along with a 95% exact binomial two-sided CI (Clopper-Pearson).

9.8.4.2.15 Responder Analysis in OL Phase in Patients with Both DM/IGT and Hypertension

In patients in the mITT-OL population, HbA1c (DM only), 2-hour plasma oGTT glucose, total daily insulin dose (DM only), mean 24-hour SBP and DBP per patient per visit will be included in the analysis. A responder will be defined as a patient who meets the above-mentioned response criteria (Section 9.8.4.2.11 and Section 9.8.4.2.14) for both conditions, or meets one of the DM or IGT response criteria with no worsening in hypertension (defined as increase in mean SBP or DBP by at least 5 mm Hg), or meet one of the uncontrolled hypertension response

criteria with no worsening in DM (defined as increase of the HbA1c by at least 0.5%) or IGT (defined as 2-hour plasma oGTT glucose >200 mg/dL). The number and percentage of patients who are responders will be presented along with a 95% exact binomial two-sided CI (Clopper-Pearson).

9.8.4.2.16 Responder Analysis by Dose in OL Phase

Responder analysis described above in Section 9.8.4.2.11, Section 9.8.4.2.14, and Section 9.8.4.2.15 will be performed for the mITT-OL population by dose at which response was first reached. Percentage of patients with response at each dose level and 95% CI will be calculated. Denominator will be the total number of all responders at OL22 and numerator will be the number of patients at each dose level when their response was first reached. Additionally, percentage of patients with response and 95% CI will be calculated for each dose level at each scheduled visit (ratio of patients with response at dose level and visit to total number of patients who reached the dose level and visit).

In patients in the mITT-OL population with hypertension at Baseline OL, the number and percentage of patients whose blood pressure normalized (SBP<130 mm Hg and DBP <80 mm Hg) at Visit OL22 will be presented along with a 95% exact binomial two-sided CI (Clopper-Pearson).

9.8.4.2.17 Response Analysis ($AUC_{glucose}$) from Baseline OL to OL22

For patients in the DM/IGT subgroup in the mITT-OL population, the proportion of patients who achieve ≥25% reduction in $AUC_{glucose}$ from Baseline OL to Visit OL22 will be summarized. The number and percentage of patients who are responders will be presented along with a 95% exact binomial two-sided CI (Clopper-Pearson). The response will be summarized separately for patients with DM/IGT, DM only, and IGT only.

9.8.4.2.18 Response Analysis (HbA1c) from Baseline OL to OL22

For patients in the DM/IGT subgroup in the mITT-OL population, the proportion of patients who achieve ≥0.5% reduction in HbA1c from Baseline OL to Visit OL22 will be summarized. The number and percentage of patients who are responders will be presented along with a 95% exact binomial two-sided CI (Clopper-Pearson). The response will be summarized separately for patients with DM/IGT, DM only, and IGT only.

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 (North America vs. ROW).

9.9 Subgroup Analyses

For primary efficacy and key secondary efficacy endpoints, the following subgroups will be considered if 10 or more patients are in each category in RW Phase:

- Intrinsic factors: Age (<45 vs. [45, 65) vs. ≥65); race; ethnicity; sex, and menopausal status (post-menopausal vs. pre-menopausal). Post-menopausal is defined as females 50 years of age or older. Pre-menopausal is defined as females less than 50 years of age.
- Extrinsic factors: (Geographic Region: North America vs. ROW).

Cushing syndrome comorbidity as described above in Section 6.10 are key subgroups of interest for subgroup analysis. Additional subgroups to be considered are:

- For secondary efficacy endpoints in RW phase, subgroup analysis will be performed by last dose received in OL phase (100 mg, 200 mg, 300 mg, and 400 mg).
- For analysis of Change from Baseline in $AUC_{glucose}$ and plasma glucose in OL phase, subgroup analysis will be performed by DM or IGT for patients with DM/IGT and also for DM/IGT patients who met response criteria and are randomized.
- For analysis of Change from Baseline in ABPM in OL phase, subgroup analysis will be performed for hypertension patients who met response criteria and are randomized.

9.10 Pharmacodynamic Analysis

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

PD measurements on fasting serum cortisol, UFC, late-night salivary cortisol, and plasma ACTH levels will be summarized. Descriptive statistics will be presented for results and change from baseline to Visit OL22 where PD blood samples were scheduled to be collected. Wilcoxon signed-rank test will also be performed to evaluate if there is a significant change from baseline to Visit OL22. Fasting serum cortisol, UFC, late-night salivary cortisol, and plasma ACTH levels will be presented separately for patients with ACTH-independent and ACTH-dependent Cushing syndrome. UFC, late-night salivary cortisol, and plasma ACTH levels are also protocol defined exploratory efficacy endpoints in Section 9.8.4.

9.11 Pharmacokinetic Analysis

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

9.12 Safety Analyses

Safety Population was defined as all patients who received at least 1 dose of study drug. All safety analyses will be performed in the OL phase Safety-OL population and the RW phase Safety-RW population.

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

9.12.1 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. In the OL phase, TEAEs will be summarized by dose level at AE onset, and overall, unless otherwise specified. Percentages are based on the number of patients who have been dosed at each dose level. In the RW phase, TEAEs will be summarized by treatment arm, and overall. Percentages are based on the number of patients in each treatment arm. Treatment emergent period for OL phase and RW phase are defined in (Section 7.1).

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

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

TEAEs assigned to CTCAE Grade 4 or 5 will be considered serious (i.e., treatment-emergent serious adverse events [TESAEs]) whether or not they are considered serious by the investigator.

Summaries that are displayed by system organ class (SOC) and preferred terms (PT) will be ordered by descending incidence of SOC and 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 in OL phase
- Overview of TEAEs by treatment arm and overall, in RW phase
- Summary of TEAEs in OL phase:
  - By SOC and PT
  - By decreasing incidence of PT
  - By SOC, PT, and maximum severity
  - By cumulative dose prior to the onset of the AE
  - EAIR by SOC and PT
- Summary of TEAEs in RW phase by treatment arm and overall:
  - By SOC and PT
  - By decreasing incidence of PT
  - By SOC, PT, and maximum severity
  - By cumulative dose prior to the onset of the AE
  - EAIR by SOC and PT
- Summary of TEAEs related to study drug by investigator assessment in OL phase:
  - By SOC and PT
  - By decreasing incidence of PT
  - By SOC, PT, and maximum severity
- Summary of TEAEs related to study drug by investigator assessment by treatment arm and overall in the RW phase:
  - By SOC and PT

    - By decreasing incidence of PT
    - By SOC, PT, and maximum severity
- Summary of treatment-emergent serious adverse events in OL phase:
    - By SOC and PT
    - By decreasing incidence of PT
    - By SOC, PT, and maximum severity
    - 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 by SOC and PT
    - With action taken of permanent discontinuation of study by SOC, PT, and maximum severity
    - Leading to study drug dose change by SOC and PT (based on exposure CRF)
    - EAIR by SOC and PT
- Summary of treatment-emergent serious adverse events by treatment arm and overall, in the RW phase:
    - By SOC and PT
    - By decreasing incidence of PT
    - By SOC, PT, and maximum severity
    - 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 by SOC and PT
    - With action taken of permanent discontinuation of study by SOC, PT, and maximum severity
    - Leading to study drug dose change by SOC and PT
    - EAIR by SOC and PT
- Summary of TEAEs with action taken of permanent discontinuation of study drug in OL phase:
    - 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 drug by treatment arm and overall in the RW phase:
    - 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 in OL phase:
    - 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 treatment arm and overall in the RW phase:
    - By SOC and PT
    - By decreasing incidence of PT
    - By SOC, PT, and maximum severity
- Summary of TEAEs by SOC and PT by comorbidity type (DM/IGT or hypertension) in OL phase as well as by treatment arm in RW phase
- TEAEs by PT occurring in at least 10% of the Safety Population in OL phase, overall and by comorbidity type
- TEAEs by PT occurring in at least 10% of the Safety Population by treatment arm and overall in RW phase, and by comorbidity type
- TEAEs by PT for PT with ≥5% difference between treatment arms in RW phase
- TEAEs with fatal outcome in OL phase
- TEAEs with fatal outcome in RW phase by treatment arm and overall
- Grade 3 or higher TEAE by SOC and PT in OL phase and RW phase
- Grade 3 or higher TEAEs related to study drug by investigator assessment, by SOC and PT in OL phase and RW phase
- TEAEs leading to dose reductions in OL phase, by SOC and PT
- TEAEs leading to dose interruptions in OL phase, by SOC and PT
- TEAEs leading to dose reductions in RW phase by treatment arm and overall, by SOC and PT
- TEAEs leading to dose interruptions in RW phase by treatment arm and overall, by SOC and PT
- Shift in CTCAE grade of TEAEs that are ongoing at the initiation of RW phase

Summaries with number of patients and percentages based on the number of patients in the Safety population that have the following adverse events will be provided:

- Overview of TEAEs in OL phase
- Summary of TEAEs in OL phase:
    - By SOC and PT
    - By decreasing incidence of PT
- Summary of treatment-emergent serious adverse events in OL phase:

  - By SOC and PT
  - By decreasing incidence of PT
- Summary of treatment-emergent serious adverse events by treatment arm and overall, in the RW phase:
  - By SOC and PT
  - By decreasing incidence of PT

At each level of summarization (e.g., any AE, SOC, and PT), patients experiencing more than one AE will be counted only once within each dose level. 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 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 by OL/RW phase. 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, also separating OL and RW phase.

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 (OL and RW phase, separately) 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:
  $$PYE = (study\ participation\ end\ date - first\ dose\ date\ )/365.25$$

Study participation end date is defined as the minimum of (the last dose date + 28 of the study phase, the start dose of RW phase (for OL Phase only), the end of study date and death date).

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

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

where $\chi^2_{\nu,a}$ is the chi-square quantile for upper tail probability on ν degrees of freedom. For the RW phase, the crude risk difference and EAIR risk difference in relacorilant and placebo along with the 95% confidence interval will be provided for TEAEs and TESAEs.

9.12.2 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 5.

The special safety topics for this analysis include:

- Excessive GR antagonism
- Adrenal insufficiency
- Irregular vaginal bleeding associated with endometrial hypertrophy
- Peripheral edema
- Renal failure
- Arterial thromboembolism
- Venous thromboembolism
- Skin neoplasms
- Neoplasms (all)
- Cardiotoxicity
- Hepatotoxicity
- Anemia
- Thrombocytopenia
- Hemorrhage
- Peripheral neuropathy
- Hyperkalemia
- Hypokalemia
- Hyperpigmentation
- New onset or exacerbation of pre-existing hypertension
- Acne
- Hyperandrogenism in females
- Hypogonadism in males

9.12.3 Deaths

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

9.12.4 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) and conventional 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 (FDA Position Statement 2013). 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, hematology, and lipid panel, will be summarized for both SI and conventional units, separately. Descriptive statistics will be presented for observed values and changes from baseline to the last post-baseline value in the OL phase and within treatment arm in the RW phase.

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

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

Hematology and chemistry results for 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 (NCI-CTCAE 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 severity grade within each dose level in OL phase
- The last observed post-baseline CTCAE grade within each dose level in the OL phase
- The worst observed severity grade by treatment arm and overall in RW phase.

Summary results will include the count and percentage of patients within each dose level in OL phase and by treatment arm in RW phase. 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.

9.12.5 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 in OL phase and RW phase.

9.12.6 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 OL phase and within treatment arm in RW phase using the average of the duplicate readings per patient per visit. 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 subjects within each shift category.

9.12.7 Physical Examination

Results of the physical examination will be presented in patient data listings by study visit, dose at time of study visit, and body system in the OL and RW phase. 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.

9.12.8 Pituitary MRI

Magnetic resonance imaging (MRI) tumor measurements (tumor volume and summation of the 3 tumor dimensions) will be summarized using descriptive statistics, to include the change from baseline to post-baseline. Change from baseline to post-baseline MRI (Increased/Decreased/Unchanged) will be summarized by frequency counts and percentages. A clinically significant volume change is defined as a change of at least 20%. A listing of MRI results by visit will be provided for each patient. Results will include tumor size categories (non-visible, microadenoma, macroadenoma), longest vertical diameter, tumor volume and change from previous MRI (Increased/Decreased/Unchanged).

9.12.9 Pregnancy Tests

Results of the pregnancy tests will be presented in patient data listings by study visit, and dose at time of study visit for OL phase and RW phase.

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/DBP at Visit RW12 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-RW population.
- All values for SBP/DBP up to the Visit RW12, will be used in the analysis regardless if they discontinue treatment (including values from retrieved dropouts).
- 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 Visit RW12 assessment is regressed on observed baseline characteristics including comorbidity type (response to DM/IGT criteria, yes vs no), height*, weight, body mass index (BMI)**, waist circumference, plasma ACTH, 24-hr UFC, late-night salivary cortisol, osteocalcin and mean 24-hour SBP and DBP from ABPM. Time on study treatment during the RW phase will also be a covariate in the model.
- 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 SBP/DBP at Visit RW12 for patients who discontinue early, but do not come back for Visit RW12 measurement with the SBP/DBP values at Visit RW12 from matched pair of patients.

* Height will not be assessed at Visit OL22. Data from Baseline OL will be used instead.

**BMI at Visit OL22 will be calculated using Height at Baseline OL and weight at Visit OL22.

APPENDIX 2

Propensity score approach will be used to impute missing data of $AUC_{glucose}$ at Visit RW12 for patients who do not take rescue medication. The step-by-step methods are described below:

- Analysis will be performed using the patients in the DM/IGT subgroup from the ITT-RW population.
- All values for $AUC_{glucose}$ up to the Visit RW12, will be used in the analysis regardless of if they discontinue treatment (including values from retrieved dropouts).
- 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 Visit RW12 assessment is regressed on observed RW baseline characteristics from Visit OL22 including comorbidity type (response to hypertension criteria, yes vs no), Comorbidity Subgroup (DM vs. IGT), height*, weight, body mass index (BMI)**, waist circumference, plasma ACTH, 24-hr UFC, late-night salivary cortisol, oGTT plasma glucose, $AUC_{glucose}$, HbA1c and osteocalcin. Time on study treatment during the RW phase will also be a covariate in the model.
- One-to-one or pair matching will be implemented, and patients will be matched within quartiles of the propensity score within the same treatment arm.
- Impute missing values of $AUC_{glucose}$ at Visit RW12 for patients who discontinue but do not come back for Visit RW12 measurement with the $AUC_{glucose}$ at Visit RW12 from the matched pair of patients.

* Height will not be assessed at Visit OL22. Data from Baseline OL will be used instead.

**BMI at Visit OL22 will be calculated using Height at Baseline OL and weight at Visit OL22.

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APPENDIX 3

Example SAS code below will be used to conduct MMRM analyses.

```
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 auc_ol22/ ddfm=kenwardroger;
 repeated visit / type=un# subject=usubjid;
 estimate "Trt diff at BL"      trt 1 -1  trt*visit 1  0  0  0  -1   0   0   0/ cl;
 estimate "Trt diff at RW4"   trt 1 -1  trt*visit 0  1  0  0   0  -1   0   0/ cl;
 estimate "Trt diff at RW8"   trt 1 -1  trt*visit 0  0  1  0   0   0  -1   0/ cl;
 estimate "Trt diff at RW12" trt 1 -1  trt*visit 0  0  0  1   0   0   0  -1/ cl;
 lsmeans trt*visit / cl;
run;
```

Go through the sequence of covariance structure as described in Section 9.8.3.2.2 if convergence criteria not met by using “un” option.

Example of SAS code for monotone regression:

```
proc mi data=bpmi out=bpmi2 nimpute=100 seed=876453 minmaxiter=200;
        class trt01pn patstype;
        var trt01pn patstype base rw4 rw8 rw12;
        monotone regression;
run;
```

APPENDIX 4

The list of medications (WHO drug preferred terms) that are considered BP medications include all terms classified under the ATC level 3 code (‘C02A’, ‘C02C’, ‘C02D’, ‘C03A’, ‘C03B’, ‘C03C’, ‘C03D’, ‘C07A’, ‘C08C’, ‘C09A’, ‘C09B’, ‘C09C’ and ‘C10A’), among which ATC level 3 code ‘C03D’ refers to mineralocorticoid antagonists medications.

APPENDIX 5

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.	Sponsor-defined PT list	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 peripheral, Peripheral swelling, Fluid retention, Skin oedema, Swelling, Skin swelling

Topic	**Definition**	**Search** Methodology	**Search** Strategy
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, 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

Topic	Definition	Search Methodology	Search Strategy
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 and narrow)
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
New onset or exacerbation of pre-existing hypertension	Clinically significant increase in arterial blood pressure	MedDRA SMQ	Hypertension (SMQ) (narrow)

Topic	**Definition**	**Search** Methodology	**Search** Strategy
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