Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Efficacy, and Pharmacokinetics of Miricorilant (CORT118335) in Obese Adult Patients with Schizophrenia or Bipolar Disorder and Recent Weight Gain While Taking Antipsychotic Medications (GRATITUDE)

NCT Number: NCT04524403

Date: 13 October 2022

STATISTICAL ANALYSIS PLAN (SAP)

Title	**A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Efficacy, and Pharmacokinetics of Miricorilant in Obese Adult Patients with Schizophrenia Taking Antipsychotic Medications (GRATITUDE II)**
Study Protocol	CORT118335-877
Phase	2
Investigational Product	Miricorilant (CORT118335)
Indication	Antipsychotic-induced Weight Gain
Protocol Version	Amendment 5
Protocol Version (date)	09 June 2022
Sponsor	Corcept Therapeutics Incorporated 149 Commonwealth Drive Menlo Park, California 94025 USA (650) 327-3270
Document Author	[redacted]
SAP Version / Date	V1.0 / 13 October 2022

Confidentiality Statement

APPROVAL SHEET

STATISTICAL ANALYSIS PLAN

CORT118335-877: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Efficacy, and Pharmacokinetics of Miricorilant in Obese Adult Patients with Schizophrenia Taking Antipsychotic Medications (GRATITUDE II)

Reviewed and Accepted at Corcept Therapeutics by

CONTRACT RESEARCH ORGANIZATION (CRO) REVIEW SHEET

STATISTICAL ANALYSIS PLAN

CORT118335-877: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Efficacy, and Pharmacokinetics of Miricorilant in Obese Adult Patients with Schizophrenia Taking Antipsychotic Medications (GRATITUDE II)

Reviewed and Accepted at [redacted]

[redacted]

LIST OF ABBREVIATIONS

Abbreviation	Definition
ACTH	adrenocorticotropic hormone
AE	adverse event
AIWG	antipsychotic-induced weight gain
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
BPRS	Brief Psychiatric Rating Scale
CGI	Clinical Global Impression Scale
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression - Severity
CI	confidence interval
COVID-19	Coronavirus disease 2019
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DBP	diastolic blood pressure
ECG	electrocardiogram
eCRF	electronic case report form
eDISH	evaluation of Drug-Induced Serious Hepatotoxicity
EE	efficacy evaluable
GGT	gamma-glutamyl transferase
GR	glucocorticoid receptor
HbA1c	glycated hemoglobin
HDL	high-density lipoprotein
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee

INR	international normalized ratio
ITT	intent-to-treat
LDL	low-density lipoprotein
LLOQ	lower limit of quantification
LOCF	last observation carried forward
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed-effect model with repeated measures
MR	mineralocorticoid receptor
NCI	National Cancer Institute
OWLQOL	Obesity Weight Loss Quality of Life Scale
PK	pharmacokinetic
PT	preferred term
REML	restricted maximum likelihood
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SI	Système International
SOC	system organ class
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
ULN	upper limit of normal
ULOQ	upper limit of quantification
W	week
WHO	World Health Organization
WRSM	Weight-Related Symptom Measure

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1 INTRODUCTION

This statistical analysis plan (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 protocol CORT118335-877, amendment 5, dated June 09, 2022: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Efficacy, and Pharmacokinetics of Miricorilant in Obese Adult Patients with Schizophrenia Taking Antipsychotic Medications (GRATITUDE II).

This SAP will be finalized before database lock 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

2.1 Overall Design

This is a Phase 2, randomized, double-blind, placebo-controlled multicenter study to evaluate the safety, efficacy, and pharmacokinetic of miricorilant in obese patients (body mass index [BMI] $\geq$30 kg/m^2) with schizophrenia currently taking olanzapine, risperidone, paliperidone, or quetiapine.

The study consists of the following study periods:

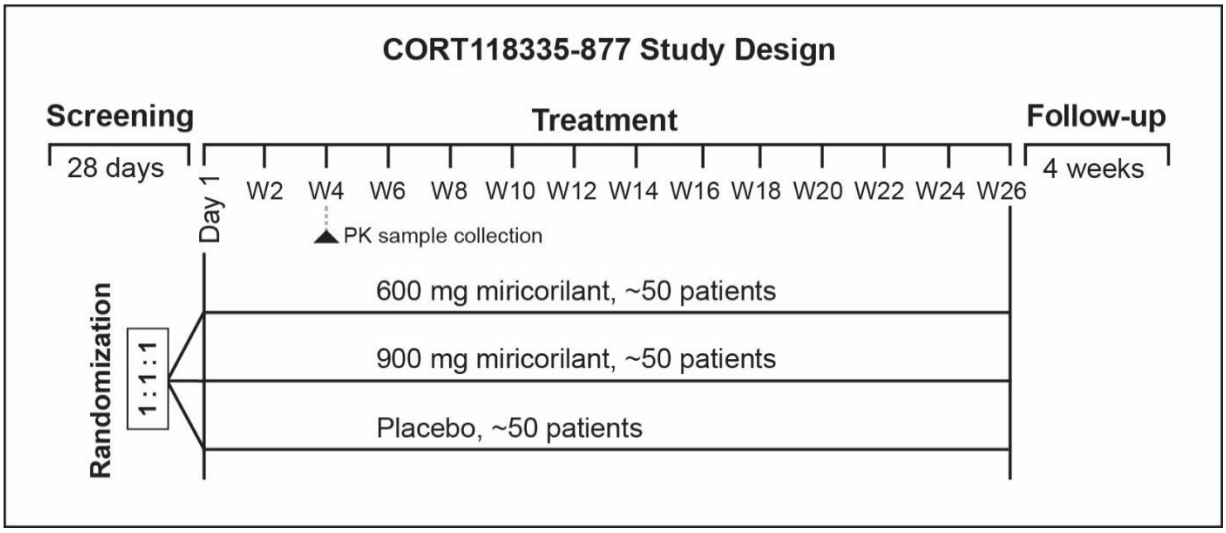
- Screening Period: up to 28 days
- Treatment Period: Day 1 (Baseline) to Week 26
- Follow-up Period: 4 weeks after last dose of study drug

Patients who are eligible for participation in the study will be randomized on Day 1 in a 1:1:1 ratio to 600 mg miricorilant, 900 mg miricorilant, or placebo, for 26 weeks of treatment.

Patients will be encouraged to volunteer for the pharmacokinetic (PK) substudy, which will be conducted at the Week 4 visit. Up to 45 patients are expected to participate. In patients who consent to participate, blood samples for the measurement of miricorilant plasma concentrations will be collected according to the PK plan.

An Independent Data Monitoring Committee (IDMC) will monitor safety during the study on a regular basis. The committee will operate independently from the sponsor and the investigators as described in the IDMC charter.

Figure 1 CORT118335-877 Study Design



Abbreviation: PK, pharmacokinetics; W, week.

3 STUDY OBJECTIVES

3.1 Primary Efficacy Objective

To assess the efficacy of both dose levels of miricorilant versus placebo in reversing antipsychotic-induced weight gain (AIWG).

3.2 Secondary Objectives

- To assess the efficacy of both dose levels of miricorilant combined versus placebo in in reversing AIWG.
- To assess the efficacy of miricorilant versus placebo in improving markers of cardiovascular risk such as waist-to-hip ratio.

3.3 Exploratory Objectives

- To assess the efficacy of miricorilant versus placebo in reversing AIWG for each subgroup of patients taking:
  - Olanzapine
  - Risperidone or paliperidone (active risperidone metabolite)
  - Quetiapine
- To assess the efficacy of miricorilant versus placebo in reducing insulin resistance in patients not treated with insulin.
- To be assessed by patient group:
  - **In all patients**, change in adrenocorticotropic hormone (ACTH), serum cortisol, serum aldosterone, Brief Psychiatric Rating Scale (BPRS), Columbia Suicide

Severity Rating Scale (C-SSRS), Clinical Global Impression (CGI) Scale, Obesity Weight Loss Quality of Life Scale (OWLQOL) and Weight-Related Symptom Measure (WRSM).
  - **In patients with diabetes**, change in glycated hemoglobin (HbA1c) and fasting blood glucose.
  - In patients with high blood pressure, change in blood pressure.
- To evaluate the dose-response relationship between miricorilant and change in body weight.
- To evaluate the exposure-response relationship between miricorilant and change in body weight.

3.4 Safety Objective

To assess the safety of miricorilant versus placebo.

3.5 Pharmacokinetic Objective

To assess the PK of both dose levels of miricorilant.

4 STUDY ENDPOINTS

4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from Baseline to Week 26 in body weight for both dose levels of miricorilant versus placebo.

4.2 Secondary Efficacy Endpoints

The following secondary endpoints will be assessed:

- Change in body weight for both dose levels of miricorilant combined versus placebo from Baseline to Week 26
- Percentage of patients achieving a ≥5% weight loss for miricorilant versus placebo from Baseline to Week 26
- Change in waist-to-hip ratio for miricorilant versus placebo from Baseline to Week 26

4.3 Exploratory Endpoints

The following exploratory endpoints will be assessed relative to Baseline:

- Change in body weight from Baseline to Week 26 for miricorilant versus placebo in each subgroup of patients taking:
  - Olanzapine
  - Risperidone or paliperidone
  - Quetiapine

- Change in Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) in patients who are not treated with insulin.

In all patients:

- Changes from Baseline to Week 26 in ACTH, serum cortisol, and serum aldosterone (pharmacodynamic assessments)
- Changes from Baseline to Week 26 in BPRS, C-SSRS, CGI, OWLQOL, and WRSM

In patients with diabetes:

- Change from Baseline to Week 26 in HbA1c
- Change from Baseline to Week 26 in fasting blood glucose.

In patients with high blood pressure:

- Change from Baseline to Week 26 in blood pressure measurements.

4.4 Safety Endpoints

Safety endpoints consist of the incidence of adverse events (AEs), treatment-emergent adverse events (TEAEs), serious TEAEs (TESAEs), and AEs leading to early discontinuation. Furthermore, safety endpoints include the changes in clinical laboratory tests, physical examinations, vital sign measurements and electrocardiogram (ECG) parameters from Baseline to Week 26.

4.5 Pharmacokinetic Endpoint

Key PK parameters will be estimated from steady-state plasma concentrations.

5 SAMPLE SIZE CONSIDERATIONS

Approximately 150 patients will be randomized 1:1:1 to 2 miricorilant treatment groups or placebo in this study. This sample size provides at least 90% power to detect a difference in body weight change of 5 kg in mean change from Baseline in body weight between either miricorilant treatment group or the placebo group. These calculations assume a common standard deviation of 6 kg and a 0.05 2-sided significance level 2-sample z-test. A drop-out rate of 40% from Baseline to Week 26 is assumed in this calculation.

Power is greater if the difference in change from Baseline in body weight between treatment and placebo is greater than 5 kg. For example, assuming there is a dose-response relationship where the difference between treatment and placebo is 6 and 7 kg in the 600 and 900 mg miricorilant groups, respectively, power would be 97% and 99% for detecting a difference between each miricorilant group and placebo.

Randomization will be stratified by the type of antipsychotic medication used (1 stratification factor with 3 levels). If ≥20 patients complete 26 weeks of treatment (10 patients treated with miricorilant and 10 patients treated with placebo) in 1 of the allowed antipsychotic medication

groups (olanzapine, risperidone or paliperidone, or quetiapine), this sample size provides 60% power to detect a difference in body weight change of 5 kg between the miricorilant and placebo groups, at alpha=0.1 level for that antipsychotic medication. The sample size estimates have not been adjusted for multiple comparisons.

6 ANALYSIS POPULATIONS

6.1 All Enrolled Population

The All Enrolled population comprises all enrolled patients.

6.2 Safety Population

The safety population comprises all patients who receive at least 1 dose of study drug. Safety data such as AEs will be summarized based on the safety population.

6.3 Intent-To-Treat (ITT) Population

The ITT population comprises all patients who are randomized to the study.

6.4 Modified Intent-To-Treat (mITT) Population

The mITT population comprises all patients who receive at least 1 dose of study drug. The mITT population contains the same patients as the safety population but will be referred to in sensitivity analyses of selected efficacy endpoints.

6.5 Efficacy Evaluable (EE) Population

The EE population comprises all patients who receive ≥4 weeks of study drug and have Baseline and at least 1 body weight measurement taken on or after Week 4. Efficacy analyses, including the primary analysis will be performed on the EE population.

Per Section 7.6, ≥4 weeks of study drug is defined as study drug duration ≥23 days. See Section 9.7 for calculation of study drug duration.

6.6 Pharmacokinetic (PK) Analysis Population

The PK population comprises all patients who have evaluable PK data.

7 DEFINITIONS, COMPUTATIONS AND CONVENTIONS

The statistical principles applied in the design and planned analyses of this study are consistent with International Council for Harmonisation (ICH) E9 guidelines (ICH 1998). All statistical analyses detailed in this SAP will be conducted using SAS version 9.4 or higher.

7.1 Definitions

Last dose date will be the last documented dose date.

Study day for efficacy will be calculated in reference to the date of first dose of miricorilant or placebo (Study Day 1). For assessments conducted on or after the first dose date, study day is calculated as (assessment date – first dose date + 1). For assessments conducted before the randomization date, study day is calculated as (assessment date – first dose date). There is no study day 0.

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

Baseline will be the assessment on the Day 1 visit if non-missing, or the last non-missing assessment prior to first dose of study drug if Day 1 visit is missing.

7.2 Reporting Conventions

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

- Mean, median, first quartile, and third quartile values will be formatted to 1 more decimal place than the measured value. Standard deviation values will be formatted to 2 more decimal places than the measured value; minimum and maximum values will be presented to the same number of decimal places as the measured value.
- Percentages will be rounded to 1 decimal place. Number and percentage values will be presented as xx (xx.x%).
- Listings will be sorted for presentation in order of patient identifier (ID), and date of procedure or event.
- 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) units with the exception of HbA1c, which will be reported using %.
- Odds ratios will be rounded to 2 decimal places.
- For by-visit observed data analyses, percentages will be calculated based on the number of patients with nonmissing data as the denominator unless otherwise specified.
- For other continuous endpoints, the summary statistics will include mean, standard deviation, first quartile, third quartile, median, and range (minimum and maximum).
- For categorical endpoints, the summary statistics will include frequency counts and percentages.
- Confidence intervals (CIs), when presented, will generally be constructed at the 95% level. For binomial variables, exact methods will be employed 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 ‘1.000’.
- Medical history and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 24.0). AE severity will be evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v.5.0).

- Prior therapies and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary and summarized by Anatomical Therapeutic Chemical (ATC) therapeutic subgroup and preferred drug names.
- For continuous values (clinical laboratory values) that are not able to be determined due to being less than the lower limit of quantification (LLOQ) or higher than the upper limit of quantification (ULOQ), the value will be assigned to 1 unit lower than the LLOQ or 1 unit higher than the ULOQ for any analyses performed. The original value will be displayed in any listings provided.

7.3 Conventions for Dates

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.
- Intervals that are presented in weeks will be transformed from days to weeks by using the following conversion formula, and rounding to 1 decimal place:
  - WEEKS = DAYS / 7
  - MONTHS = DAYS / 30.4375
  - YEARS = DAYS / 365.25

Detailed rules for imputation of missing/partially missing dates for AEs, prior/concomitant medications/procedures, and schizophrenia diagnosis are provided in Section 12.1.

7.4 Treatment Group Presentation

Patient disposition, protocol deviations, demographics and Baseline characteristics, medical history, prior medications and procedures, and efficacy data summaries will be presented by randomized treatment group. Unless otherwise specified, safety data summaries will be presented by the actual treatment received.

7.5 Handling of Missing Data

Unless stated otherwise, missing data will not be replaced with imputed values.

Missing dates or partially missing dates will be imputed conservatively for AEs and prior/concomitant medications/procedures. Specific rules for handling of missing or partially missing dates for date of birth, AEs, prior/concomitant medications/procedures, and diagnosis of schizophrenia are provided in Section 12.1.

7.6 Analysis Visit Windows

In analysis of data summarized by study visit, unscheduled and early termination visits will be reassigned a study visit where data is scheduled for collection based on the actual days relative to Baseline (Table 1). If multiple visits fall in the analysis visit window, the one closest to the target day will be used. If two visits are equidistant to the target day, then the later visit will be used.

Table 1 Analysis Visit Windows for Assessments

Visit Name	Start Day	Target Day	End Day
Screening	Date of informed consent	-28	-1
Baseline	—	1	—
Week 2	2	15	22
Week 4	23	29	36
Week 6	37	43	50
Week 8	51	57	64
Week 10	65	71	78
Week 12	79	85	92
Week 14	93	99	106
Week 16	107	113	120
Week 18	121	127	134
Week 20	135	141	148
Week 22	149	155	162
Week 24	163	169	176
Week 26	177	183	200
Follow-up	> Study day of last dose of study drug	Study day of last dose of study drug +28	—

Note: Any unscheduled, early termination or follow-up visits will be assigned to a Baseline – Week 26 analysis visit as priority if it fits within the window, regardless of whether the visit was after last dose of study drug. Otherwise, it will be considered for the follow-up analysis visit.

8 TIMING OF ANALYSES

8.1 Interim Analysis

No interim analyses are planned for this study.

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.

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 (Apr 2003).

All efficacy summaries will be presented by treatment group as randomized. All safety summaries will be presented by actual treatment group. In addition, data will be tabulated for all patients combined. All relevant data collected on the electronic case report form (eCRF) will be presented in by-patient data listings, to include the site identifier, patient number, antipsychotic medication and assigned treatment group.

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

9.2 Patient Disposition

Participant disposition will show the number of patients who have been enrolled, in ITT, safety and EE analysis populations, took study drug, discontinued treatment, discontinued from the study, reasons for discontinuations (including if due to Coronavirus disease 2019 [COVID-19]), completed 26 weeks of study treatment, completed the study, and completed the follow-up study visit.

9.3 Protocol Deviations

Protocol deviations will be categorized as important or other according to the protocol deviation specification document. Important protocol deviations that occur during the study will be summarized by deviation category for all patients in the ITT and safety population by treatment group as randomized. A by-patient listing of important protocol deviations will be provided.

Patient eligibility including inclusion and exclusion criteria that were not met at randomization will be summarized for all patients in the ITT population.

9.4 Demographic and Baseline Characteristics

The following demographic characteristics will be presented for the ITT, safety and EE populations in listings, and summarized by treatment and overall:

- Age at informed consent (continuous and categorical variable: ≥18 to <30, ≥30 to <50, ≥50 to ≤65) will be summarized
- Sex
- Of childbearing potential (Yes/No)
- Ethnicity
- Race

Additionally, Baseline characteristics including height, weight, BMI, BMI category (obesity class 1 [30-34.9 kg/m^2], obesity class 2 [35-39.9 kg/m^2], extreme obesity class 3 [≥ 40 kg/m^2]), time on current antipsychotic medication (months), antipsychotic medication used (olanzapine, risperidone/paliperidone, or quetiapine), HOMA-IR score, ACTH, serum cortisol, serum

aldosterone, BPRS, C-SSRS, CGI-S, OWLQOL, WRSM, time from schizophrenia diagnosis to enrollment (years), and waist-to-hip ratio will be summarized. BMI will be calculated as: weight (kg) / [height (cm) / 100]^2. Time (years) since diagnosis will be calculated as (the randomization date − the diagnosis date +1)/365.25. The imputation rules for missing or partial diagnosis dates are described in Section 12.1.

9.5 Medical History

Medical history will be summarized for all patients in the ITT and safety populations. Frequency counts and percentages to summarize patients reporting medical history by system organ class (coded using MedDRA version 24.0 or above) and schizophrenia history will be presented.

9.6 Prior and Concomitant Medications and Subsequent Therapies

Medications will be coded using the WHO Drug Global B3 version March 2020 or above. Medications entered on the eCRF will be mapped to ATC drug class (level 4) and generic drug name (preferred drug name).

A prior medication is defined as any medication administered 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 and up to the last dose date. Medications administered after the last dose date are defined as subsequent therapies. A medication may be defined as more than one medication classification (prior, concomitant, or subsequent). The imputation rules for missing start and end date of a concomitant medication are described in Section 12.1.

The proportion of patients who received prior, concomitant, and subsequent therapies or medications will be summarized separately for the ITT and safety populations. For all table summaries, the number and percentage of patients receiving any medication will be summarized by treatment group and overall. The preferred drug name and the preferred drug name within ATC drug class will be summarized separately and displayed by descending order of incidence. Patients reporting use of more than one medication at each level of summarization (any medication received, ATC class, and preferred drug name) will be counted only once. The medication classification (e.g., prior, concomitant, subsequent, or a combination of classification) will be presented on the listing of prior, concomitant, and subsequent medications.

Additionally, for patients who have diabetes on entry to the trial, prior, concomitant, and subsequent medications related to diabetes will be listed. Similarly, for patients with high blood pressure at Baseline as defined in Section 9.8.4.14, prior, concomitant, and subsequent antihypertensive medications will be listed.

9.7 Extent of Exposure and Study Drug Compliance

All recorded information on oral dosing of miricorilant, including kit number, actual dose, start and end date, any dose modifications and related reason will be presented in a data listing sorted by start date of administration.

A table by treatment arm and overall will provide summary statistics on the following:

- Duration of Exposure: The duration of exposure for each study drug will be presented in days and calculated as:

  Duration = Expected date of last dose − Date of the first dose + 1.

  Expected date of last dose will be the latest of either the last dose date or the last missed dose date.

- Total Dose Received: The total dose received for each study drug will be:

  Total Dose Received = Total tablets dispensed – Total tablets returned.

- Total Dose Expected: A subject will have an expected dose determined by the earliest start date and the latest end date times six tablets taken daily. For subjects where their dose received is either zero or missing, an associated expected dose is included in the total dose expected derivation. Therefore, the total dose expected to be taken is:

  Total Dose Expected = Duration of Exposure x 6.

- Compliance: Compliance is calculated for each study drug as:

  Compliance = (Total Dose Received/ Total Dose Expected) x 100.

A by-patient listing including the study drug start date, study drug end date, number of pills taken, number of pills expected to be taken, and overall compliance will be produced.

9.8 Efficacy Analyses

9.8.1 Multiplicity Adjustment for Efficacy Analyses

Each efficacy endpoint will be evaluated at the 2-sided 0.05 level of significance without adjustment for multiplicity of testing. P-values from secondary and exploratory tests will be considered descriptive.

9.8.2 Primary Efficacy Analysis

The primary endpoint is used to evaluate the primary objective of assessing the efficacy of each of the 2 miricorilant doses (600 mg and 900 mg) compared with placebo in reversing AIWG caused by an oral or injectable second-generation antipsychotic medication.

The primary endpoint will be assessed using a mixed-effect model with repeated measures (MMRM). An MMRM analysis refers to a restricted maximum likelihood (REML)-based, mixed-effects repeated measures analysis using all longitudinal observations at each scheduled post-Baseline visit. That is the change in body weight at each visit will be assessed using an MMRM model with Baseline body weight as a continuous covariate; antipsychotic medication (olanzapine, risperidone/paliperidone, or quetiapine), randomized treatment (600 mg or 900 mg miricorilant, or placebo), visit, and treatment-by-visit interaction as fixed, categorical effects. The difference in body weight change between each of the 2 miricorilant doses (600 mg and 900 mg) and placebo will be estimated from the model along with its 95% CI. The primary analysis will be performed on the EE population.

In more detail, the Baseline body weight is reported in kg and measured at the Day 1 (Baseline) visit and at 8 post-Baseline visits: Weeks 2, 4, 6, 10, 14, 18, 22, and 26, in patients who consented to any protocol versions. If the weight from the Day 1 visit is missing, then the weight from the screening visit will be used for the Baseline weight. For each patient, the outcome variable for the MMRM is the arithmetic difference between the Baseline body weight and Baseline body weight and the weight at each post-Baseline visit. Specifically, the outcome variable, Y_{kl}, at visit $k, k = 1, \dots, 9$, for the l^{th} patient is

$$Y_{kl} = W_{kl} - W_{bl}$$

where W_{kl} is the weight measured at visit k for the l^{th} patient, where $k = 1$ is the Baseline visit, and W_{bl} is the Baseline weight for the l^{th} patient.

A retrieved dropout approach will be used to provide outcome measurements for patients who discontinue treatment prematurely. Specifically, patients will be asked to continue the study visits and assessments after discontinuation of study medication. Patients who return for weight measurements after the discontinuation of study medication will be referred to as 'retrieved dropouts'.

For patients who discontinue early and do not return for weight measurements, the body weight from the early termination visit, follow-up visit or an unscheduled visit, if available, will be mapped to the analysis visit window as outlined in Section 7.6, and will be used in analysis.

For patients who discontinue treatment earlier than Week 26, do not have weight measurements available after treatment discontinuation, and therefore have missing data ("non retrieved dropouts"), no imputations will be used. The missing at random assumption is implied.

The expected value of the primary analysis model can be written

$$E[Y_{ijkl}] = \mu + \alpha W_{bl} + \beta_i + \gamma_j + \delta_k + (\gamma\delta)_{jk}$$

where

- μ is the overall mean
- α is the effect of body weight at Baseline
- $\beta_i, i = 1,2,3$ is the effect of background antipsychotic medication (olanzapine, risperidone/paliperidone, or quetiapine)
- $\gamma_j, j = 1,2,3$ is the effect of randomized treatment (600 mg miricorilant, 900 mg miricorilant, or placebo)
- $\delta_k, k = 1, \dots, 9$ is the effect of visit k
- $(\gamma\delta)_{jk}$, $j = 1,2,3; k = 1, \dots, 9$, is the interaction between treatment j and visit k.

There are 2 tests of hypotheses in this trial:

1. Is there a difference in body weight change from Baseline to Week 26 (i.e., at the eighth post-Baseline visit) between 600 mg miricorilant and placebo. The null and alternative hypotheses for this question can be written, in terms of model parameters:

$$H_0: \gamma_1 + (\gamma\delta)_{1,9} - \left(\gamma_3 + (\gamma\delta)_{3,9}\right) = 0$$

vs

$$H_1: \gamma_1 + (\gamma\delta)_{1,9} - \left(\gamma_3 + (\gamma\delta)_{3,9}\right) \neq 0,$$

2. Is there a difference in body weight change from Baseline to Week 26 (i.e., at the eighth post-Baseline visit) between 900 mg miricorilant and placebo. The null and alternative hypotheses for this question can be written, in terms of model parameters:

$$H_0: \gamma_2 + (\gamma\delta)_{2,9} - \left(\gamma_3 + (\gamma\delta)_{3,9}\right) = 0$$

vs

$$H_1: \gamma_2 + (\gamma\delta)_{2,9} - \left(\gamma_3 + (\gamma\delta)_{3,9}\right) \neq 0.$$

The analysis will be performed using SAS PROC MIXED (Section 12.2). Restricted maximum likelihood estimation (REML) will be used to fit the model. An unstructured covariance structure will be used to model the within-patient errors. The Kenward-Roger approximation will be used to estimate degrees of freedom.

The primary hypothesis will be assessed using a linear contrast to estimate the difference in body weight change at Week 26 between each of the 2 miricorilant doses and placebo along with its 95% confidence interval (CI). The estimated difference, its 95% CI, and its associated p-value will be presented. Sample SAS code to implement the model is provided in the Section 12.2.

If the model does not converge with both the Hessian and the G matrix being positive definite under the default fitting algorithm used by PROC MIXED, the Fisher scoring algorithm will be implemented by specifying the SCORING option in SAS. If the model still does not converge, the following covariance structures will be used until the convergence criteria is met, in this order: Toeplitz, first-order autoregressive, heterogeneous compound symmetry, and compound symmetry. Both the Toeplitz and autoregressive structures assume that observations on the same patient are more closely related when they are closer in time. The autoregressive structure is a special case of the Toeplitz structure that requires fewer parameters to be estimated. The compound symmetry assumes the variances are homogeneous (i.e., there is a correlation between 2 separate measurements, but it is assumed that the correlation is constant regardless of how far apart the measurements are).

The least squares mean and 95% CI of the change from Baseline at Week 26 will also be estimated from the model for each treatment group. No adjustment for multiplicity will be applied.

9.8.2.1 Supportive Analyses

The primary analysis model (Section 9.8.2) will also be used to estimate the difference between treatment groups at each of other 7 post-Baseline visits, specifically Weeks 2, 4, 6, 10, 14, 18, and 22. The comparisons will be specified using linear contrasts analogous to that used to compare treatment groups at Week 26. The estimated difference between groups, its 95% CI, and its associated nominal p-value will be presented for each visit. No adjustments will be made for multiplicity.

In addition to model estimates, descriptive statistics, including 95% CIs, will summarize weight at each visit by treatment group, and weight change and percent weight change group at each post-Baseline visit. Statistics for any visit will be calculated from all patients who had weight measurements at the visit. The full set of descriptive statistics will be presented tabularly. The mean weight change per group and its 95% CI from MMRM will be graphed, with time in weeks on the x-axis and change in body weight from MMRM on the y-axis. A similar graph of the mean weight per treatment group over time will be produced. Additionally, mean percent change from Baseline in body weight will be presented graphically along with 95% CI (sourced from the t-distribution) for each treatment group and visit.

9.8.2.2 Sensitivity Analyses

The primary analysis uses all data observed (including data from retrieved dropouts) and a missing at random assumption for non-retrieved dropouts (the patients with missing body weight at Week 26). Retrieved dropouts are patients who discontinue study treatment before Week 26 and return for measurement of body weight at the time of the pre-scheduled visit up to Week 26. Non-retrieved dropouts are patients who discontinue study treatment before Week 26 and do not return for the measurement of body weight after study discontinuation.

As a sensitivity analysis, the primary analysis model as described in Section 9.8.2 will also be performed in mITT population. Like the primary analysis, this sensitivity analysis will use supplied retrieved dropout data without imputation at Week 26.

A second sensitivity analysis will rerun the primary analysis model as described in Section 9.8.2, without using retrieved dropout data. Weight measurements will be considered missing at random for any visit after a patient discontinues treatment.

Moreover, for patients who do not have body weight at Week 26 (non-retrieved dropouts), their change in body weight from Baseline to Week 26 will be imputed with the treatment group mean change in body weight from Baseline to Week 26, derived from retrieved dropouts (the patients who return for Week 26 assessment after early treatment discontinuation). If there is no retrieve dropout data at Week 26 in a specific arm, then no imputation will be applied within the same arm.

Lastly, following protocol amendment 3 and thereafter, body weight is collected biweekly. In more detail, body weight is measured at the Day 1 (Baseline) visit and at 13 post-Baseline visits: Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 and 26. We will rerun the modified primary analysis model utilizing all available Baseline and post-Baseline visit data, where visit $k = 1, \ldots, 14$. The analysis will be carried out in the EE population with the following options:

1. Using retrieve dropout data with imputation for patients who do not have data at Week 26
2. Using retrieve dropout data without imputation at Week 26
3. Without retrieve dropout data

The complete list of all analyses of the primary endpoint is included in Table 2. The difference between each of the 2 miricorilant doses and placebo in body weight change at Week 26 will be estimated for each sensitivity analysis. The estimated difference will be accompanied by its 95%

CI and associated p-value. The least squares means for each treatment group at Week 26, along with their 95% CIs, will also be estimated.

Table 2 List of Statistical Analyses of the Primary Endpoint

Analysis	Population	Study Visits	Retrieved Dropouts	Imputation for Non-Retrieved Dropouts at Week 26
Primary analysis	EE	Baseline, Weeks 2, 4, 6, 10, 14, 18, 22, and 26	Included	No imputation; MAR for missing data at Week 26
Sensitivity analysis 1	mITT	Baseline, Weeks 2, 4, 6, 10, 14, 18, 22, and 26	Included	No imputation; MAR for missing data at Week 26
Sensitivity analysis 2	EE	Baseline, Weeks 2, 4, 6, 10, 14, 18, 22, and 26	Included	Yes, mean of retrieved dropouts within treatment arm at Week 26
Sensitivity analysis 3	EE	Baseline, Weeks 2, 4, 6, 10, 14, 18, 22, and 26	Excluded	No imputation; MAR for missing data
Sensitivity analysis 4	EE	Baseline, Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, and 26	Included	No imputation; MAR for missing data at Week 26
Sensitivity analysis 5	EE	Baseline, Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, and 26	Included	Yes, mean of retrieved dropouts within treatment arm at Week 26

Sensitivity analysis 6	EE	Baseline, Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, and 26	Excluded	No imputation; MAR for missing data

EE, efficacy-evaluable; MAR, missing at random; mITT, modified intent-to-treat.

9.8.3 Secondary Efficacy Analyses

9.8.3.1 Change from Baseline in Body Weight for Both Dose Levels of Miricorilant Combined vs Placebo

For the first secondary endpoint, the 2 miricorilant dose groups will be combined into a single treatment group and assessed using a similar model as the MMRM for the primary analysis (Section 9.8.2). The other factors in the model will remain the same. The difference in body weight change at Week 26 between the combined miricorilant treatment groups and placebo will be estimated from the model along with its associated 95% CI and associated p-value. The least squares means for the combined treatment group and placebo at Week 26, along with their 95% CIs, will also be estimated.

In addition to model estimates, descriptive statistics, including 95% CIs, will summarize weight at each visit by treatment group, and weight change and percent weight change group at each post-Baseline visit. Statistics for any visit will be calculated from all patients who had weight measurements at the visit. The full set of descriptive statistics will be presented tabularly and a subset will also be graphed. Specifically, the mean weight change per group and its 95% CI from MMRM will be graphed with time in weeks on the x axis and change in body weight from MMRM on the y-axis. A similar graph of the mean weight per treatment group over time will be produced. Additionally, mean percent change from Baseline in body weight for all visits will be presented graphically along with 95% CI (sourced from the t-distribution) for each treatment group and visit.

9.8.3.2 Responders Achieving a ≥ 5% Weight Loss

The second secondary efficacy endpoint is the percentage of patients achieving a ≥5% weight loss from Baseline at Week 26 for each of the 2 miricorilant doses versus placebo. The endpoint requires calculation of the percent change in body weight from Baseline to Week 26 for each patient. For the l^{th} patient, the percent change is calculated as

$$Z_{week\ 26,l} = 100 \times \left(W_{week\ 26,l} - W_{bl}\right)/W_{bl}$$

where $W_{week\ 26,l}$ is the weight measured at Week 26 for the l^{th} patient, and W_{bl} is the Baseline weight for the l^{th} patient.

The outcome variable will be a binary variable indicating a patient as a responder, that is whether the l^{th} patient achieved a ≥5% weight loss from Baseline:

$$\theta_l = \begin{cases} 1 \text{ if } Z_{week\ 26,l} \leq -5 \\ 0 \text{ otherwise} \end{cases}.$$

As with the primary analysis, a retrieved dropout approach will be used for patients who discontinue treatment prior to their Week 26 visit. Those patients will be asked to return for their Week 26 visits, and the weight measurement at that visit will be used to calculate the percent change from Baseline.

For patients who discontinue early and do not supply retrieved dropout data, the body weight from the early termination visit, follow-up visit or an unscheduled visit, if available and within the analysis visit window of Week 26, will be assigned as the weight measured at Week 26 when calculating the percent change in body weight. Otherwise, the last available weight measurement will be substituted for the weight measured at Week 26. This is equivalent to a last observation carried forward (LOCF) approach.

A logistic regression model with Baseline value as a continuous covariate, and background antipsychotic medication and treatment group as factors will be used to compare each of the 2 miricorilant doses to placebo. The analysis will be performed on the EE population.

A sample of SAS code that can be used to implement the logistic regression model is provided in the Section 12.2. The p-value comparing treatment to placebo, as well as the odds ratio and its 95% CI, will be reported from the model.

In addition to the model results, the percentage of patients in each treatment group who lose ≥5% of their Baseline body weight by week will be presented along with its 95% CI. The CI will be calculated using the Exact method. Descriptive statistics for the percent change from Baseline are described in Section 9.8.2.1.

9.8.3.3 Waist-to-Hip Ratio

The third secondary efficacy endpoint is the change from Baseline in waist-to-hip ratio at Week 26 for each of the 2 miricorilant doses versus placebo. The waist-to-hip ratio will be calculated as the ratio of the circumference of the waist to the hip. The change in waist-to-hip ratio will be analyzed using the MMRM model described in Section 9.8.2 with Baseline waist-to-hip ratio as a continuous covariate; antipsychotic medication (olanzapine, risperidone/paliperidone, or quetiapine), randomized treatment (600 mg or 900 mg miricorilant, or placebo), visit, and treatment-by-visit interaction as fixed, categorical effects. The difference between each of the 2 miricorilant doses and placebo group at Week 26 will be estimated from the model along with its 95% CI and associated p-value. The analysis will be performed on the EE population and all observed data (including retrieved dropout data) will be used. Data for non-retrieved dropouts will not be imputed for the analysis of this variable. A sample of SAS code that can be used to implement the MMRM model is provided in the Section 12.2.

The same MMRM will also be used to estimate the difference between treatment groups at each of other 7 visits from Week 2 through Week 22. The comparisons will be specified using linear contrasts analogous to that used to compare treatment groups at Week 26. The estimated difference between groups, its 95% CI, and its associated p-value will be presented for each visit.

Descriptive statistics will summarize the waist-to-hip ratio by treatment group for all visits and the percent change from Baseline in waist-to-hip ratio by treatment group for all post-Baseline visit. The change from Baseline in waist-to-hip ratio by treatment group and 95% CI from MMRM will be graphed with time in weeks on the x-axis and MMRM estimated change in waist-to-hip ratio on the y-axis. Additionally, the mean percent change in waist-to-hip ratio at each visit, along with 95% CI (sourced from the t-distribution), will be graphed for each treatment group with time in weeks on the x-axis and percent change from Baseline on the y-axis.

9.8.4 Exploratory Analyses

9.8.4.1 Antipsychotic Medication Subgroup Analysis

Change in body weight for each of the two miricorilant doses versus placebo and combined miricorilant treatment group versus placebo in each subgroup of patients taking olanzapine, risperidone or paliperidone, and quetiapine will be analyzed. The subgroup analysis for change from Baseline in body weight to each week will be conducted using MMRM. Retrieve dropout data will be used for patients who discontinue treatment early. Data for non-retrieve dropouts will not be imputed. The same MMRM model as described in Section 9.8.2 will be performed on each subset of patients in the EE population who are taking olanzapine, risperidone or paliperidone, and quetiapine. A sample of SAS code that can be used to implement the MMRM model is provided in the Section 12.2.

9.8.4.2 Body Mass Index Subgroup Analysis

Change in body weight for each of the two miricorilant doses versus placebo will be analyzed in each BMI subgroup, including obesity class 1 (30-34.9 kg/m^2), obesity class 2 (35-39.9 kg/m^2), extreme obesity class 3 ($\geq$ 40 kg/m^2). The subgroup analysis for change from Baseline in body weight to each week will be conducted using MMRM. Retrieve dropout data will be used for patients who discontinue treatment early. Data for non-retrieve dropouts will not be imputed. The same MMRM model as described in Section 9.8.2 will be performed on each subset of patients in the EE population. A sample of SAS code that can be used to implement the MMRM model is provided in the Section 12.2.

9.8.4.3 Homeostatic Model Assessment for Insulin Resistance

HOMA-IR will be calculated for each patient at Baseline and Week 26 using the approximate formula (Matthews et al. 1985):

$$\text{HOMA-IR} = (\text{fasting plasma glucose (mg/dL)} \times \text{fasting insulin } (\mu\text{U/mL}))/405.$$

Each of the 2 miricorilant doses will be compared to placebo on the difference in HOMA-IR between Week 26 and Baseline using a Wilcoxon rank-sum test on the EE population. For patients who discontinue early, HOMA-IR from the early termination visit or an unscheduled visit, if available and within the analysis visit window of Week 26, will be used in place of missing Week 26 results. Data for non-retrieve dropouts will not be imputed.

Descriptive statistics will summarize HOMA-IR by treatment group for all visits and the percent change from Baseline in HOMA-IR by treatment group for all post-Baseline visit. The median percent change in HOMA-IR at each visit will be graphed as box plots for each treatment group with time in weeks on the x-axis and percent change from Baseline on the y-axis. Similar plots will be generated for median change in HOMA-IR at each visit.

9.8.4.4 Adrenocorticotropic Hormone

ACTH will be measured at Baseline and Week 26. Each of the 2 miricorilant doses compared to placebo will be assessed using analysis of covariance (ANCOVA) models that include the change in the endpoint between Baseline/Day 1 and Week 26 as the outcome variable, Baseline body weight as a covariate, and antipsychotic medication and randomized treatment as factors. The outcome variable will be the difference between ACTH at Week 26 and the ACTH value at Baseline. All observed data will be included in the analysis (including retrieved dropout data). Data for non-retrieved dropouts will not be imputed. The analysis will be performed on the EE population.

The estimated least squares mean, standard error, and its associated p-value, as well as the estimated difference in the least squares means, its 95% CI, and its associated p-value will be presented.

Descriptive statistics will summarize ACTH by treatment at Baseline/Day1 and Week 26 and the change from Baseline in ACTH by treatment at Week 26.

9.8.4.5 Serum Cortisol

Like ACTH, serum cortisol will be measured at Baseline and Week 26. Each of the 2 miricorilant doses will be compared to placebo on the change from Baseline in serum at Week 26 using the same method and model as ACTH. All observed data will be included in the analysis (including retrieved dropout data at Week 26). Data for non-retrieved dropouts will not be imputed.

Descriptive statistics will summarize serum cortisol by treatment at Baseline/Day 1 and Week 26 and the change from Baseline in serum cortisol by treatment at Week 26.

9.8.4.6 Serum Aldosterone

Serum aldosterone will be measured at Baseline and Week 26. Each of the 2 miricorilant doses will be compared to placebo on the change from Baseline in serum aldosterone at Week 26 using the same method and model as ACTH. All observed data will be included in the analysis (including retrieved dropout data at Week 26). Data for non-retrieved dropouts will not be imputed.

Descriptive statistics will summarize serum aldosterone by treatment at Baseline/Day 1 and Week 26, and the change from Baseline in serum aldosterone by treatment at Week 26.

9.8.4.7 Brief Psychiatric Rating Scale

The BPRS is a scale used to track changes in schizophrenia symptoms over time. The scale involves an interview of the patient by the Investigator and includes 24 different symptom areas in which the Investigator ranks the severity of each symptom using a scale of 1 (symptom is absent) to 7 (symptom is severe). The BPRS total score is calculated by adding together the scores from the 24 individual symptom areas. Higher scores indicate more severe pathology. It will be assessed at every visit.

The change from Baseline in the BPRS total score will use the MMRM analysis as described in Section 9.8.2 to assess the difference between each of the 2 miricorilant doses and placebo. The outcome variable will be the difference between the total BPRS score at each post-Baseline visit and the total BPRS value at Baseline. Retrieve dropout data will be used for patients who discontinue treatment early. Data for non-retrieve dropouts will not be imputed. The analysis will be performed on the EE population.

A linear contrast will estimate the difference between each of the 2 miricorilant doses and placebo in the change in BPRS total score at Week 26. The estimated difference, its 95% CI, and its associated p-value will be presented. A sample of SAS code that can be used to implement the MMRM model is provided in the Section 12.2.

Descriptive statistics will summarize the BPRS total score by treatment at each visit and the change from Baseline in BPRS total score by treatment at each post-Baseline visit. The mean change from Baseline in BRPS total score, along with its 95% CI from MMRM, will be graphed for each treatment group with time in weeks on the x-axis and change from Baseline from MMRM on the y-axis.

9.8.4.8 Obesity Weight Loss Quality of Life Scale and Weight-Related Symptom Measure

Health-related quality of life scores will be measured using self-reported OWLQOL questionnaire and WRSM. Both the OWLQOL and the WRSM are intended to be administered together. The 17-item OWLQOL measures behavior and feelings that are associated with obesity and weight loss using a 7-point response scale that ranges from 0 “not at all” to 6 “a very great deal”. The WRSM is a 20-item measure of the symptoms associated with obesity and obesity treatment, along with the degree to which each symptom “bothers the individual”. The questionnaires will be completed from Baseline until Follow-up and should always be conducted prior to dosing when conducted on study drug administration days.

The change from Baseline in the OWLQOL total score and the WRSM total score will use the MMRM analysis as described in Section 9.8.2 to assess the difference between each of the 2 miricorilant doses and placebo. The outcome variable will be the difference between the total score at each post-Baseline visit and the total score at Baseline. The analysis will be performed on the EE population for each questionnaire separately. Retrieve dropout data will be used for patients who discontinue treatment early. Data for non-retrieve dropouts will not be imputed.

A linear contrast will estimate the difference between each of the 2 miricorilant doses and placebo in the change in the total score at Week 26. The estimated difference, its 95% CI, and its associated p-value will be presented. A sample of SAS code that can be used to implement the MMRM model is provided in the Section 12.2.

Descriptive statistics will summarize the OWLQOL and WRSM total scores by treatment at each visit and the change from Baseline in the total scores by treatment at each post-Baseline visit for each questionnaire separately. The mean change from Baseline in the OWLQOL and WRSM total score, along with its 95% CI from MMRM, will be graphed for each treatment group with time in weeks on the x-axis and change from Baseline from MMRM on the y-axis.

9.8.4.9 Columbia-Suicide Severity Rating Scale

The C-SSRS is a suicidal ideation rating scale used to evaluate suicidality (Posner et al. 2011). The C-SSRS consists of a series of questions to patients that can help identify patients at risk for suicide, assess the severity and immediacy of that risk, and gauge the level of support the patient may need.

Suicidal ideation is defined as a "yes" response to any of the five suicidal ideation questions (wish to be dead, non-specific active suicidal thoughts, active suicidal ideation with any methods (not plan) without intent to act, active suicidal ideation with some intent to act, without specific plan, or active suicidal ideation with specific plan and intent).

Suicidal behavior is defined as a "yes" response to any of the five suicidal behavior questions (actual attempt, interrupted attempt, aborted attempt, preparatory acts or behavior, or suicide).

C-SSRS suicidal ideation, suicidal behavior and suicidal ideation or behavior will be summarized as dichotomous variables by treatment at each visit for the safety population separately for patients with schizophrenia and bipolar disorder. A shift table will be provided to demonstrate changes in C-SSRS categories from Baseline to the worst post-Baseline category (suicidal behavior being considered worse than suicidal ideation).

The suicidal ideation intensity rating is defined as the sum of the five intensity item scores (frequency, duration, controllability, deterrents, and reasons for ideation) to create a total score (range 0 to 25) to represent the intensity rating. If the patient did not endorse any suicidal ideation, set the intensity rating to 0. The suicidal ideation intensity rating score will be listed.

9.8.4.10 Clinical Global Impression-Severity

The CGI, used to assess the patient's global functioning, is comprised of two scales: the CGI-Severity scale (CGI-S), which assesses illness severity, and the CGI-Improvement scales (CGI-I), which assesses change from the initiation of treatment. The CGI-S asks the Investigator one question: "Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?", which is rated on the following 7-point scale: 1=normal, not at all ill; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among the most extremely ill patients. CGI-S will be measured at Baseline.

Descriptive statistics will summarize the CGI-S score at Baseline.

9.8.4.11 Clinical Global Impression-Improvement

The CGI-I comprises one question to the investigator: "Compared to the patient's condition at Baseline, this patient's condition is: 1=very much improved since the initiation of treatment; 2=much improved; 3=minimally improved; 4=no change from Baseline (the initiation of treatment); 5=minimally worse; 6=much worse; 7=very much worse since the initiation of treatment."

Note that the CGI-I inherently incorporates change from Baseline into its scores. Thus, the scores themselves are used to evaluate change from Baseline with no need to explicitly calculate the difference from Baseline. The Baseline score is still used in the CGI-I analysis but only as a covariate in the analysis model.

To assess the exploratory CGI-I endpoint, the numerical results from the CGI-I will be treated as a continuous variable and an MMRM similar to that described in Section 9.8.2 will be used to assess the difference between each of the 2 miricorilant doses and placebo at Week 26. The difference is the outcome variable will be the CGI-I score at each post-Baseline visit. Other aspects of the model such as the fitting algorithm, covariance structure, and degrees of freedom are the same as for the primary analysis. The analysis will be performed on the EE population. A sample of SAS code that can be used to implement the MMRM model is provided in the Section 12.2.

Descriptive statistics will summarize the CGI-I score by treatment at each visit.

The CGI-I will also be summarized as a dichotomous variable where a positive response is defined as having a score of 1 (very much improved), 2 (much improved) and 3 (minimally improved). The number and percentage of patients with a positive response will be presented by treatment group for each post-Baseline visit. Fisher's exact tests will be used to compare the treatment groups on the percent with a positive response at each visit.

9.8.4.12 HbA1c in Patients with Diabetes

The analysis described here will be performed on the subset of patients in the EE population who have diabetes on entry to the trial. Measurements of HbA1c will be obtained at screening, Baseline/Day 1, Week 14, and Week 26. Miricorilant (600mg and 900mg) will be compared to placebo on the difference in HbA1c between Week 26 and Baseline using pairwise Wilcoxon rank-sum tests. All observed data for HbA1c will be used in the analysis (including retrieved dropout data). Non-retrieved dropout data for Week 26 will not be imputed.

Descriptive statistics will summarize HbA1c by treatment at Baseline and Week 26 and the change from Baseline in HbA1c by treatment at Week 26.

Similarly, descriptive statistics and Wilcoxon rank-sum test will be provided separately for patients with an HbA1c $< 6.5\%$, $6.5\% \leq$ HbA1c $< 8.0\%$, and an HbA1c $\geq 8.0\%$ at Baseline regardless of whether the patient has diabetes on entry to the trial, assuming at least 10 patients

per group. If there are less than 10 patients for a given group, then only descriptive statistics will be provided for that group.

9.8.4.13 Fasting Blood Glucose in Patients with Diabetes

The analysis described here is analogous to that described for HbA1c and will be performed on the subset of patients in the EE population who have diabetes on entry to the trial and have fasting blood glucose measurements at Baseline and Week 26. Each of the 2 miricorilant doses will be compared to placebo on the difference in fasting blood glucose between Week 26 and Baseline using a Wilcoxon rank-sum test. For patients who discontinue early, fasting plasma glucose measured at the early termination visit, follow-up visit or an unscheduled visit, if available and within the analysis window of Week 26 as outlined in Section 7.6, will be used in place of missing Week 26 results. Data from non-retrieved dropouts will not be imputed.

Descriptive statistics will summarize fasting blood glucose by treatment at Baseline and Week 26 and the change from Baseline in fasting blood glucose by treatment at Week 26.

9.8.4.14 Blood Pressure in Patients with High Blood Pressure

The analysis described here will be performed on the subset of patients in the EE population who have high blood pressure at the Baseline visit. High blood pressure is based on the limits for Stage 1 hypertension defined in the 2017 guideline developed by the American College of Cardiology and American Heart Association (Whelton et al. 2017). Specifically, a patient will be considered to have high blood pressure if they satisfy any of the following criteria regardless of position (seated, supine, or standing):

- Baseline systolic blood pressure (SBP) is $\geq$ 130 mm Hg,
- Baseline diastolic blood pressure (DBP) $\geq$ 80 mm Hg, or
- if being treated with an antihypertensive medication at Baseline or has medical history of hypertension.

Vital signs, including systolic blood pressure (SBP) and diastolic blood pressure (DBP), will be measured at every visit. Descriptive statistics will summarize SBP and DBP by treatment at Baseline and each post-Baseline visit. The difference in SBP and DBP at each visit and their corresponding Baseline values will be calculated and summarized by treatment group for each post-Baseline visit. The significance of the difference between groups in change from Baseline will be assessed using a pair of Wilcoxon rank-sum tests – one comparing groups on change in SBP and the second comparing groups on change in DBP – at each visit.

9.9 Safety Analyses

All safety analyses will be performed in the safety population. All safety data will appear in by-patient data listings. Unless specified otherwise, the categorical safety analyses will include both scheduled and unscheduled visits.

9.9.1 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.

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

Summaries that are displayed by system organ class (SOC) and preferred terms (PT) will be ordered by alphabetical order of SOC and by descending incidence of PT nested within each SOC. 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 AEs will be provided:

- Overview of AEs
- Summary of TEAEs
- Summary of TEAEs related to study drug
- Summary of TEAEs leading to dose interruption
- Summary of TEAEs related to study drug leading to dose interruption
- Summary of TEAEs leading to dose discontinuation
- Summary of TEAEs related to study drug leading to dose discontinuation
- Summary of Serious TEAEs
- Summary of Serious TEAEs related to study drug
- Summary of Serious TEAEs leading to dose discontinuation
- Summary of TEAEs with fatal outcome
- Summary of TEAEs with Grade 3 or higher
- Summary of TEAEs related to study drug with Grade 3 or higher
- Summary of TEAEs of excessive glucocorticoid receptor (GR) or mineralocorticoid receptor (MR) antagonism (Protocol Section 5.3.2)

All above summaries will be presented by PT, by PT nested within SOC, and by maximum severity. TEAEs and TESAEs will also be presented by decreasing incidence of PT per 100 patient years of exposure, calculated as (number of subjects with events/total patient-years)×100, where patient-years is the sum of exposure patient-years (days / 365.25) of all patients within the treatment group.

All AEs, whether treatment-emergent or not, will be listed by treatment arm and individual patient, including dates of onset and resolution and associated study day, duration, serious, NCI-CTCAE grade (CTCAE v.5.0), action taken, outcome, and relationship to study drug. TESAEs and TEAEs leading to discontinuation will also be listed separately.

9.9.2 Deaths

All deaths during the study, including the Follow-up period, will be listed including the primary cause of death.

9.9.3 Clinical Laboratory Tests

All descriptive summaries of laboratory results will be based on data analyzed by the central laboratory and presented in SI units. 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, laboratory test, unit laboratory value, normal ranges, and abnormal category (e.g. high, low, abnormal).

Clinical laboratory measurements, including chemistry and hematology, will be summarized by visit. Descriptive statistics will be presented for observed values as well as change from Baseline for all post-Baseline visits for the Treatment and Follow-up periods. Shift from Baseline CTCAE grade to worst post-Baseline grade, as well as shift from Baseline abnormal category (below normal, normal, above normal) to lowest and to highest post-Baseline category will be provided.

Additionally, a summary of the number of patients with liver test abnormalities will be provided for the worst value after first dose of study drug including alanine aminotransferase (ALT; >3x upper limit of normal [ULN], >5xULN, >8xULN, >10xULN, and >20xULN), aspartate aminotransferase (AST; >3xULN, >5xULN, >8xULN, >10xULN, and >20xULN), total bilirubin (>ULN and >2xULN), alkaline phosphatase (ALP; >1.5xULN), ALT or AST >3xULN and total bilirubin (>1.5xULN and >2xULN), and ALT or AST>3xULN and international normalized ratio (INR) >1.5. A listing of all patients with liver test abnormalities will be provided including all laboratory values and corresponding abnormality. For ALT, AST, total bilirubin, ALP and gamma-glutamyl transferase (GGT), the mean and 95% CI (sourced from t-distribution) per treatment group will be graphed with time in weeks on the x-axis and lab value on the y-axis. Furthermore, an evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) graph will be provided.

9.9.4 Vital Signs

Vital sign parameter measurements, including SBP and DBP, heart rate, respiratory rate, and body temperature, will be summarized. Descriptive statistics will be presented for results, as well as change from Baseline to the last post-Baseline value for the Treatment and Follow-up periods.

9.9.5 Electrocardiograms

Twelve-lead ECG interval parameters will be summarized. Descriptive statistics will be presented for observed values as well as change from Baseline for all post-Baseline visits for the Treatment and Follow-up periods using the average of the triplicate readings per patient per visit.

Twelve-lead ECG results will be classified as “normal” and “abnormal.” A listing of ECG results will be provided including visit, date, and interpretation results.

9.9.6 Physical Examination

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

9.9.7 Pregnancy Tests

Results of the pregnancy tests will be presented in patient data listings by study visit.

9.10 Other Exploratory Analyses

Additional exploratory efficacy/safety analyses will be conducted as deemed necessary.

9.10.1 Responders Achieving a ≥7% and ≥10% Weight Loss

A responder is defined as a patient achieving ≥7% and ≥10% weight loss, respectively, and will be determined as described in Section 9.8.3.2. Similar to the secondary efficacy endpoint, the binary responder outcome will be analyzed using a logistic regression model as described in Section 9.8.3.2. A sample of SAS code that can be used to implement the logistic regression model is provided in the Section 12.2.

9.10.2 Fasting Lipids

Fasting lipids (triglycerides, low-density lipoprotein [LDL], high-density lipoprotein [HDL], total cholesterol) will be summarized by visit using the safety population. Descriptive statistics will be presented for observed values as well as change from Baseline for all post-Baseline visits for the Treatment and Follow-up periods.

9.11 COVID-19 Infection

Information regarding visits that are affected by COVID-19 pandemic are being collected on the eCRF. A listing of visits that are affected by COVID-19 pandemic will be provided. Additionally, a listing of protocol deviations associated with COVID-19 and an AE listing of patients with a positive diagnosis of COVID-19 infection will be provided. Any additional analyses determined to be appropriate for patients impacted by COVID-19 pandemic will be performed as deemed necessary.

Summaries of protocol deviations associated with COVID-19 will be provided for all enrolled patients. A summary of subjects with visits affected by COVID-19 will be provided for all enrolled patients.

9.12 Pharmacokinetic Analyses

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

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.

The Protocol specifies that HOMA-IR will be analyzed using similar models as the primary analysis of body weight change (i.e. MMRM), and that it may be log-transformed prior to analysis. However, HOMA-IR is only collected at one post-Baseline visit, so MMRM is not appropriate. Wilcoxon rank-sum test is used instead, and it is done without log-transformation of the data.

Similarly, the protocol specifies that CGI-S will be analyzed using MMRM. However, CGI-S is only collected at Baseline. Therefore, CGI-S will be summarized descriptively at Baseline.

11 REFERENCES

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12 APPENDIX

12.1 Imputation of Missing/Partially Missing Dates

For AEs 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 AEs.

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

- If both Month and Day are missing and Year = Year of treatment start date, then set to treatment start date.
- If both Month and Day are missing and Year ≠ Year of treatment start date, then set to January 1.
- If Day is missing and Month and Year = Month and Year of treatment start date, then set to treatment start date.
- If Day is missing and Month and Year ≠ Month and Year of treatment start date, then set to first of the month.
- If start date is completely missing, set to treatment start date as long as adverse event end date is not prior to treatment start date.

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

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

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

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

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

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.

When the diagnosis date of schizophrenia is missing, the 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.

12.2 Sample SAS Code

A sample SAS code to implement the MMRM model is as follows. The MMRM model is described in Section 9.8.2. The Baseline covariate and outcome variable may differ for each analysis, refer to associated section for more details.

```
proc mixed data=Data;
  class patient antipsyc treat visit;
  model chg = base antipsyc treat visit treat*visit /ddfm=KR;
  repeated visit / subject=patient type=un;
  lsmeans treat*visit /cl; *Get change lsm estimates at Wk 26;
  estimate 'Miricorilant - Placebo at Week 26'
    treat 1 -1
    treat*visit 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 -1 /cl; *diff at Wk
26;
run;
```

A sample of SAS code that can be used to implement the logistic regression model is as follows. The code assumes the reference group, i.e., the placebo patients, comes first in the parameterization of the data.

```
proc logistic data=WtData;
  class antipsyc treat (ref=first) / param=glm;
  model WtXPct (event="1") = wtbase antipsyc treat;
  lsmeans treat / diff oddsratio cl;
run;
```

where WtXPct is the responder variable as determined in Section 9.8.3.2.