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: NCT03818256

Date: 27 July 2022

STATISTICAL ANALYSIS PLAN (SAP)

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)**
Study Protocol	CORT118335-876
Phase	2
Investigational Product	Miricorilant (CORT118335)
Indication	Antipsychotic-Induced Weight Gain
Protocol Version	Amendment 5
Protocol Version (date)	11 January 2022
Sponsor	Corcept Therapeutics Incorporated 149 Commonwealth Drive Menlo Park, California 94025 USA (650) 327-3270
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Confidentiality Statement

APPROVAL SHEET

STATISTICAL ANALYSIS PLAN

CORT118335-876: 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)

Reviewed and Accepted at Corcept Therapeutics by

[redacted]

CONTRACT RESEARCH ORGANIZATION (CRO) REVIEW SHEET

STATISTICAL ANALYSIS PLAN

CORT118335-876: 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)

Reviewed and Accepted at [redacted] by

[redacted]

LIST OF ABBREVIATIONS

Abbreviation	Definition
ACTH	adrenocorticotropic hormone
AIWG	antipsychotic-induced weight gain
AE	adverse event
ALT	alanine aminotransferase
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
CRO	contract research organization
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
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
INR	international normalized ratio
IWRS	interactive web response system
LDL	low-density lipoprotein

Abbreviation	Definition
LLOQ	lower limit of quantification
LOCF	last observation carried forward
MADRS	Montgomery-Asberg depression rating scale
MAR	missing at random
MedDRA	medical dictionary for regulatory activities
MMRM	mixed-effect model with repeated measures
MR	mineralocorticoid receptor
PD	pharmacodynamic
PK	pharmacokinetic
PT	preferred term
REML	restricted maximum likelihood
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SDTM	Study Data Tabulation Model
SI	Système International
SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
ULOQ	upper limit of quantification
VLDL	very low-density lipoprotein
WHO	World Health Organization
YMRS	Young mania rating scale

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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 CORT118335-876, amendment 5, dated January 11, 2022: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Efficacy, and Pharmacokinetics (PK) of Miricorilant (CORT118335) in Obese Adult Patients with Schizophrenia or Bipolar Disorder and Recent Weight Gain While Taking Antipsychotic Medications (GRATITUDE).

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 CSR 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 PK of miricorilant in obese patients (BMI ≥30 kg/m^2) with schizophrenia or bipolar disorder who have recent antipsychotic-induced weight gain (AIWG) caused by any oral or injectable second-generation antipsychotic medication (except clozapine) within the last 18 months prior to Screening.

The study consists of the following study periods:

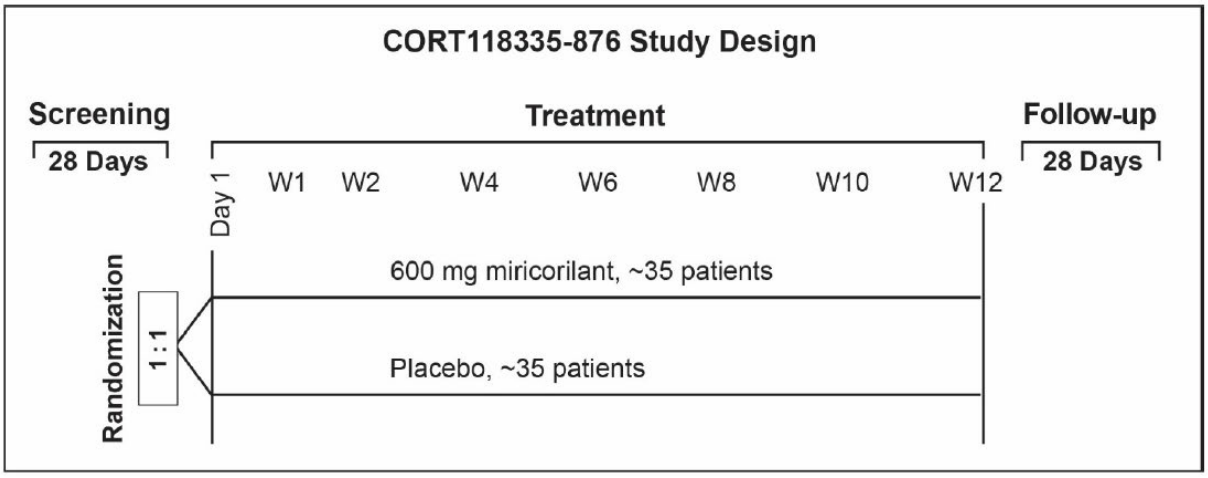
- Screening Period: up to 28 days
- Treatment Period: Day 1 to Week 12
- Follow-up Period: 4 weeks after last study dose (Week 16)

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

Patients will be asked to volunteer for the PK substudy, and up to 45 patients are expected to provide PK samples as part of this substudy. The PK substudy will be conducted at the Week 4 visit. In those patients who consent to participate in the substudy, blood samples will be collected according to the PK plan outlined in the study manual.

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 CORT118335-876 Study Design



Abbreviation: W, week.

3 STUDY OBJECTIVES

3.1 Primary Efficacy Objective

To assess the efficacy of miricorilant compared with placebo in reversing recent AIWG caused by an atypical antipsychotic medication.

3.2 Secondary Objective

To assess the efficacy of miricorilant in improving metabolic parameters associated with diabetes or cardiovascular morbidity.

3.3 Safety Objective

To assess the safety of miricorilant with concurrent administration of an atypical antipsychotic medication.

3.4 Pharmacokinetic Objective

To assess the PK of miricorilant in patients with recent AIWG caused by an atypical antipsychotic medication.

4 STUDY ENDPOINTS

4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in body weight at Week 12 for 600 mg miricorilant versus (vs) placebo.

4.2 Secondary Efficacy Endpoints

The efficacy of 600 mg miricorilant vs placebo in improving metabolic parameters will be measured by

- Percentage of patients achieving a ≥ 5% body weight loss from baseline at Week 12
- Change from baseline in waist-to-hip ratio at Week 12
- Change from baseline in Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) at Week 12

4.3 Exploratory Endpoints

Exploratory endpoints are listed by associated population.

In all patients:

- Change from baseline in adrenocorticotropic hormone (ACTH) at Week 12, and
- Change from baseline in serum cortisol at Week 12.

In patients with schizophrenia:

- Changes from baseline in Brief Psychiatric Rating Scale (BPRS), Columbia-Suicide Severity Rating Scale (C-SSRS), and Clinical Global Impression scale (CGI) at Week 12.

In patients with bipolar disorder:

- Changes from baseline in C-SSRS, CGI, Young Mania Rating Scale (YMRS), and the Montgomery-Asberg Depression Rating Scale (MADRS) at Week 12.

In patients with diabetes:

- Change from baseline in glycated hemoglobin (HbA1c) at Week 12, and
- Change in fasting plasma glucose at Week 12.

In patients with high blood pressure:

- Change from baseline in blood pressure measurements at Week 12.

4.4 Safety Endpoints

Safety endpoints consist of the incidence of adverse events (AEs), treatment-emergent adverse events (TEAEs), serious TEAEs, and AEs leading to early discontinuation. Furthermore, safety endpoints include the change from baseline in clinical laboratory tests, physical examinations, vital sign measurements and electrocardiogram (ECG) parameters at Week 12.

4.5 Pharmacokinetics Endpoint

PK assessments will be summarized in the PK/pharmacodynamic (PD) SAP.

5 SAMPLE SIZE CONSIDERATIONS

Approximately 70 patients will be randomized 1:1 to treatment or placebo in this study. This sample size provides 90% power to detect a difference in body weight change of 4 kg between the 600 mg miricorilant dose group and the placebo group. Based on Larsen et al. 2017, which examined the effect of liraglutide on olanzapine-and clozapine-treated patients, as well as on other studies of AIWG summarized in Mizuno et al. 2014, a standard deviation (SD) of around 4 to 5 kg can be expected for the difference in body weight change between treatment groups. Accordingly, a SD of 4.5 kg is assumed here. Assuming a difference in body weight change between groups of 4 kg with an SD of 4.5 kg, and setting α=0.05, 28 patients per group provides 90% power to detect a significant difference between active dose group and placebo after completing 12 weeks of treatment.

Allowing for 20% dropouts increases the required sample size to 35 patients per group for a total of 70 patients in the trial.

With 35 patients receiving 600 mg miricorilant in the trial, there is an 83% chance that an uncommon AE (i.e., an AE expected to occur in only 1 in every 20 patients) will be observed at least once during the trial. If a specific AE is never seen in the trial, the 95% upper confidence bound on its true incidence would be 10%.

Randomization will be stratified by the type of antipsychotic medication used (olanzapine, risperidone/paliperidone, quetiapine, aripiprazole, or other). If at least 14 patients complete 12 weeks of treatment (7 patients treated with 600 mg miricorilant and 7 patients treated with placebo) in one of the allowed antipsychotic medications, this sample size provides 50% power to detect a difference in body weight change of 4 kg between 600 mg miricorilant and placebo, at alpha=0.1 level for that stratum of antipsychotic medication.

6 ANALYSIS POPULATIONS

6.1 All Enrolled Population

The All Enrolled population comprises all patients who meet study enrollment criteria.

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 on the safety population.

6.3 Intent-To-Treat (ITT) Population

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

6.4 Efficacy Evaluable (EE) Population

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.

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

6.5 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 first dose date, study day is calculated as (assessment date − first dose date 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. SD 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 Système 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, SD, median, first quartile, third quartile, 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 '<.0001' and p-values that round to 1.000 will be presented as '1.000'.
- Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA v 23.0. 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 Global B3 (September 2019) version 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 one unit lower than the LLOQ or one 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. date format in SAS).
- Dates recorded in comment fields will not be imputed or reported in any specific format.
- Intervals that are presented in weeks, months, or years will be transformed from days 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 or bipolar disorder 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 or bipolar disorder are provided in Section 12.1.

7.6 Analysis Visit Windows

In analyses of data summarized by study visit, if a scheduled visit is missing then unscheduled, early termination, and follow-up 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 1	2	8	11
Week 2	12	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
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 12 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, and assigned treatment group.

In general, continuous variables will be summarized by the number of patients with non-missing data, mean, 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 All Enrolled, Safety, ITT and EE analysis population, took study drug, discontinued treatment, discontinued treatment but continued with remaining scheduled visits, discontinued from the study, reasons for discontinuations (including if due to Coronavirus disease 2019 [COVID-19]), completed 12 weeks of study treatment, completed the study, and completed the follow-up study visit.

Completion of the follow-up study visit is defined as completing the date of visit eCRF for the follow-up 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 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 All Enrolled populations in listings, and summarized by treatment and overall in All Enrolled, Safety and EE populations:

- 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, body weight, body mass index (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, quetiapine, aripiprazole, or other), HOMA-IR score, ACTH, serum cortisol, BPRS, C-SSRS, CGI-S, MADRS, YMRS, time from schizophrenia diagnosis to enrollment (years), time from bipolar disorder diagnosis to enrollment (years), and waist-to-hip ratio will be summarized. BMI will be calculated as: body 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.

The demographic and baseline characteristics will also be summarized separately for patients diagnosed with schizophrenia or bipolar disorder using the Safety population. Only those measurements associated with the given disorder will be presented.

9.5 Medical History

Medical history will be summarized for all patients in the All Enrolled and Safety population. Frequency counts and percentages to summarize patients reporting medical history by system organ class (SOC) (coded using MedDRA version 23.0).

Schizophrenia and bipolar disorder medical history will be presented separately.

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.

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 and including the last dose date. Medications newly

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 Safety population. 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 alphabetical order of ATC and descending order of incidence for the preferred drug name within ATC. 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 at baseline, prior, concomitant, and subsequent medications related to diabetes will be listed. Similarly, for patients with high blood pressure at baseline as defined in Section 9.8.4.11, 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 and placebo, 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:

  $$\text{Duration} = \text{date of last dose} - \text{Date of the first dose} + 1.$$

- Total Tablets Received: The total tablets received for each study drug will be:

  $$\text{Total Tablets Received} = \text{Total tablets dispensed} - \text{Total tablets returned}.$$

- Total Tablets Expected: A patient will have an expected number of tablets determined by the earliest start date and the latest end date times six tablets taken daily. For patients 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:

  $$\text{Total Tablets Expected} = \text{Duration of Exposure} \times 6.$$

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

  $$\text{Compliance} = (\text{Total Tablets Received} / \text{Total Tablets Expected}) \times 100.$$

A by-patient listing including the study drug start date, study drug end date, number of tablets taken, number of tablets 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 miricorilant compared with placebo in reversing AIWG caused by an atypical 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 baseline and each scheduled post-baseline visit. That is the change in body weight at baseline and each post-baseline visit will be assessed using an MMRM model with baseline body weight as a continuous covariate; antipsychotic medication (olanzapine, risperidone/paliperidone, quetiapine, aripiprazole, or other), randomized treatment (600 mg miricorilant or placebo), visit, and treatment-by-visit interaction as fixed, categorical effects. The difference in body weight change between miricorilant 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 7 post-baseline visits: Weeks 1, 2, 4, 6, 8, 10, and 12. If the body weight from the day 1 visit is missing, then the body weight from the last non-missing assessment prior to the first dose of study drug will be used for the baseline body 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 body weight at each post-baseline visit. Specifically, the outcome variable, Y_{kl}, at visit $k, k = 1, \ldots, 8$, for the l^{th} patient is

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

where W_{kl} is the body weight measured at visit k for the l^{th} patient, where k =1 is the baseline visit, and W_{bl} is the baseline body 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 12, 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 (MAR) 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
- $\beta_i, i = 1,2,3,4,5$ is the effect of background antipsychotic medication (olanzapine, risperidone/paliperidone, quetiapine, aripiprazole, or other)
- $\gamma_j, j = 1,2$, is the effect of randomized treatment (placebo or 600 mg miricorilant, respectively)
- $\delta_k, k = 1, \dots, 8$ is the effect of visit k
- $(\gamma\delta)_{jk},\ j = 1,2; k = 1, \dots, 8$, is the interaction between treatment j and visit k.

The primary hypothesis tests whether there is a difference in change body weight change at Week 12 between miricorilant and placebo:

$$H_0: \gamma_1 + (\gamma\delta)_{1,8} - \left(\gamma_2 + (\gamma\delta)_{2,8}\right) = 0$$

$$H_1: \gamma_1 + (\gamma\delta)_{1,8} - \left(\gamma_2 + (\gamma\delta)_{2,8}\right) \neq 0.$$

The analysis will be performed using SAS PROC MIXED (Section 12.2). 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 12 between miricorilant and placebo along with its 95% 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 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 (TOEP), first-order autoregressive [AR(1)], heterogeneous compound symmetry (CSH), and compound symmetry (CS). 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. There is a correlation between two 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 12 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 baseline and each of other 6 post-baseline visits from Week 1 through Week 10. The comparisons will be specified using linear contrasts analogous to that used to compare treatment groups at Week 12. The estimated difference between groups, its 95% CI, and its associated p-value will be presented for each visit. No adjustments will be made for multiplicity.

In addition to model estimates, descriptive statistics will summarize body weight at each visit by treatment group, and body weight change and percent body weight change group at each post-baseline visit. Statistics for any visit will be calculated from all patients who had body 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 body weight change per treatment group and 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 body weight per treatment group over time will be produced with 95% CI (sourced from the t-distribution). 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 MAR assumption for non-retrieved dropouts (the patients with missing body weight at Week 12). Retrieved dropouts are patients who discontinue study treatment before Week 12 and return for measurement of body weight at the time of the pre-scheduled visit up to Week 12. Non-retrieved dropouts are patients who discontinue study treatment before Week 12 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 ITT population. Like the primary analysis, this sensitivity analysis will use supplied retrieved dropout data without imputation at Week 12.

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 MAR for any visit after a patient discontinues treatment.

Moreover, for patients who do not have body weight at Week 12 (non-retrieved dropouts), their change in body weight from Baseline to Week 12 will be imputed with the treatment group mean change in body weight from Baseline to Week 12, derived from retrieved dropouts (the patients

who return for Week 12 assessment after early treatment discontinuation). If there is no retrieve dropout data at Week 12 in a specific arm, then no imputation will be applied within the same arm.

The complete list of all analyses of the primary endpoint is included in Table 2. The difference between miricorilant and placebo in body weight change at Week 12 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 12, along with their 95% CIs, will also be estimated.

Table 2 List of statistical analyses of the primary endpoint

Analysis	Population	Retrieved dropouts	Imputation for non-retrieved dropouts at Week 12
Primary analysis	EE	Included	No imputation; MAR for missing data at Week 12
Sensitivity analysis 1	ITT	Included	No imputation; MAR for missing data at Week 12
Sensitivity analysis 2	EE	Excluded	No imputation; MAR for missing data
Sensitivity analysis 3	EE	Included	Yes, mean of retrieved dropouts within treatment arm at Week 12

9.8.3 Secondary Efficacy Analyses

9.8.3.1 Responders Achieving a ≥ 5% Body Weight Loss

The first secondary efficacy endpoint is the percentage of patients achieving a ≥ 5% body weight loss from baseline at week 12 for 600 mg miricorilant vs placebo. The endpoint requires calculation of the percent change in body weight from baseline to week 12 for each patient. For the l^{th} patient, the percent change is calculated as

$$Z_{week\ 12,l} = \left(\left(W_{week\ 12,l} - W_{bl}\right)/W_{bl}\right) \times 100$$

where $W_{week\ 12,l}$ is the body weight measured at week 12 for the l^{th} patient, and W_{bl} is the baseline body 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% body weight loss from baseline:

$$\theta_l = \begin{cases} 1 \text{ if } Z_{week\ 12,l} \leq -5 \\ 0 \text{ otherwise} \end{cases}.$$

As with the primary analysis, a retrieved dropout approach will be used for patients who discontinue treatment prior to their Week 12 visit. Those patients will be asked to return for their Week 12 visits, and the body 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 12 as outlined in Section 7.6, will be assigned for the body weight measured at Week 12 when calculating the percent change in body weight. Otherwise, the last available body weight measurement will be substituted for the body weight measured at Week 12. 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 miricorilant 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 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.

9.8.3.2 Waist-to-Hip Ratio

The second secondary efficacy endpoint is the change from baseline in waist-to-hip ratio at Week 12 for 600 mg miricorilant vs placebo. The waist-to-hip ratio will be calculated as the ratio of the circumference of the waist to the hip. The waist-to-hip ratio will be analyzed using the MMRM model described in Section 9.8.2. The difference between miricorilant and placebo at Week 12 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 retrieved dropout data will be used, when possible, for patients who discontinue the trial early. 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 baseline and each of other 6 visits from Week 1 through Week 10. The comparisons will be specified using linear contrasts analogous to that used to compare treatment groups at Week 12. 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 change and 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.

9.8.3.3 Homeostatic Model Assessment for Insulin Resistance

HOMA-IR will be calculated for each patient at Baseline and Week 12 using the approximate formula (Matthews et al. 1985):

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

Miricorilant will be compared to placebo on the difference in HOMA-IR between Week 12 and baseline using a Wilcoxon rank-sum test on the EE population. For patients who discontinue early, HOMA-IR from the early termination visit, follow-up visit, or an unscheduled visit, if available and within the analysis visit window as outlined in Section 7.6, will be used in place of missing Week 12 results. Data for non-retrieved dropouts will not be imputed.

Descriptive statistics will summarize HOMA-IR by treatment group for all visits and the change and 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 Exploratory Analyses

9.8.4.1 Adrenocorticotropic Hormone

ACTH will be measured at baseline, Week 4, and Week 12. Miricorilant will be compared to placebo on the change from baseline in ACTH at Week 12 using the MMRM model described in Section 9.8.2. The outcome variable will be the difference between ACTH at baseline and each post-baseline visit and the ACTH value at baseline. Retrieved dropout data will be used for patients who discontinue treatment early. Data for non-retrieved dropouts will not be imputed. The analysis will be performed on the EE population.

A linear contrast analogous to that used in the primary analysis will estimate the difference between miricorilant and placebo in the change in ACTH at Week 12. 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 ACTH by treatment at each visit and the change from baseline in ACTH by treatment at each post-baseline visit. The mean ACTH, 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 on the y-axis.

9.8.4.2 Serum Cortisol

Like ACTH, serum cortisol will be measured at baseline, Week 4, and Week 12. Miricorilant will be compared to placebo on the change from baseline in serum at Week 12 using the same method and model as ACTH (Section 9.8.4.1) with only two differences: (1) baseline serum

cortisol will replace serum ACTH as a continuous covariate in the model; and (2) the outcome variable will be the difference between serum cortisol at baseline and each post-baseline visit and the serum cortisol value at baseline. Data for non-retrieved dropouts will not be imputed. 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 serum cortisol by treatment at each visit and the change from baseline in serum cortisol by treatment at each post-baseline visit. The mean serum cortisol, 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 on the y-axis.

9.8.4.3 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 miricorilant and placebo. Baseline BPRS total score will be incorporated into the model as the continuous baseline covariate. The outcome variable will be the difference between the total BPRS score at baseline and each post-baseline visit and the total BPRS value at baseline. Data for non-retrieved dropouts will not be imputed. The analysis will be performed on the EE population for patients with schizophrenia.

A linear contrast will estimate the difference between miricorilant and placebo in the change in BPRS total score at Week 12. 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 baseline and each post-baseline visit. The mean change from baseline in BPRS 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 on the y-axis.

9.8.4.4 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 or 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.

9.8.4.5 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.

The numerical results from the CGI-S will be treated as a continuous variable. The MMRM described in Section 9.8.2 will be used to assess the difference between miricorilant and placebo in the change from baseline in CGI-S at Week 12. Baseline CGI-S will be incorporated into the model as the continuous baseline covariate. The outcome variable will be the difference between the CGI-S score at baseline and each post-baseline visit and the CGI-S score at baseline. Data for non-retrieved dropouts will not be imputed. 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-S score by treatment at each visit and the change from baseline in CGI-S score by treatment at each post-baseline visit.

Additionally, the MMRM analysis and descriptive statistics summary table will be presented separately for patients diagnosed with schizophrenia or bipolar disorder using the EE population.

9.8.4.6 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 CGI-S 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 miricorilant and placebo at Week 12. 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. Data for non-retrieved dropouts will not be imputed. The analysis will be performed on the EE population.

Descriptive statistics will summarize the CGI-I score by treatment at each visit. Additionally, the MMRM analysis and descriptive statistics summary table will be presented separately for patients diagnosed with schizophrenia or bipolar disorder using the EE population.

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.

9.8.4.7 Montgomery-Asberg Depression Rating Scale

The MADRS is a ten-item diagnostic questionnaire used by psychiatrists to measure the severity of depressive episodes in patients with mood disorders. The questionnaire includes questions on the following symptoms: 1) Apparent sadness 2) Reported sadness 3) Inner tension 4) Reduced sleep 5) Reduced appetite 6) Concentration difficulties 7) Lassitude 8) Inability to feel 9) Pessimistic thoughts 10) Suicidal thoughts. Each question yields a score from 0–6; higher MADRS score indicates more severe depression. A total MADRS score will be determined as the sum of the individual scores (range 0 to 60).

The change from baseline in the MADRS score will use the MMRM analysis as described in Section 9.8.2 to assess the difference between miricorilant and placebo. Baseline MADRS score will be incorporated into the model as the continuous baseline covariate. The outcome variable will be the difference between the total MADRS score at baseline and each post-baseline visit and the total MADRS value at baseline. Data for non-retrieved dropouts will not be imputed. The analysis will be performed on the EE population for patients with bipolar disorder. 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 MADRS score by treatment at each visit and the change from baseline in MADRS score by treatment at each post-baseline visit.

9.8.4.8 Young Mania Rating Scale

The YMRS is a clinical interview scale to assess the severity of manic states. The scale has eleven items and is based on the patient's subjective report of his or her clinical condition. The purpose of each item is to rate the severity of that abnormality in the patient, making it useful for continuous evaluations of manic symptoms. It can help guide clinicians on treatment planning and progress. A total YMRS score will be determined as the sum of the individual scores (range 0 to 60).

The change from baseline in the YMRS score will use the MMRM analysis as described in Section 9.8.2 to assess the difference between miricorilant and placebo. Baseline YMRS will be incorporated into the model as the continuous baseline covariate. The outcome variable will be the difference between the total YMRS score at baseline and each post-baseline visit and the total YMRS value at baseline. Data for non-retrieved dropouts will not be imputed. The analysis will be performed on the EE population for patients with bipolar disorder.

Descriptive statistics will summarize the YMRS score by treatment at each visit and the change from baseline in YMRS score by treatment at each post-baseline visit.

9.8.4.9 HbA1c in Patients with Diabetes

The analysis described here will be performed on the subset of patients in the EE population who have diabetes at baseline. Measurements of glycated hemoglobin (HbA1c) will be obtained at screening, baseline, and Week 12. Miricorilant will be compared to placebo on the difference in HbA1c between Week 12 and baseline using a Wilcoxon rank-sum test. For patients who discontinue early, HbA1c from the early termination visit, follow-up visit, or an unscheduled visit, if available and within the analysis visit window as outlined in Section 7.6, will be used in place of missing Week 12 results. Data for non-retrieved dropouts will not be imputed.

Descriptive statistics will summarize HbA1c by treatment at baseline and Week 12 and the change from baseline in HbA1c by treatment at Week 12.

Similarly, descriptive statistics and Wilcoxon rank-sum test will be provided separately for patients with an HbA1c $< 6.5\%$, $6.5\% \leq$ HbA1c $< 8\%$, and an HbA1c $\geq 8\%$ at baseline regardless of whether the patient has diabetes at baseline, 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.

9.8.4.10 Fasting Plasma 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 at baseline. Fasting plasma glucose measurements will be obtained at baseline and Week 12. Miricorilant will be compared to placebo on the difference in fasting plasma glucose between Week 12 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 visit window as outlined in Section 7.6, will be used in place of missing Week 12 results. Data for non-retrieved dropouts will not be imputed.

Descriptive statistics will summarize fasting plasma glucose by treatment at baseline and Week 12 and the change from baseline in fasting plasma glucose by treatment at Week 12.

9.8.4.11 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 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 ≥ 130 mm Hg,
- baseline diastolic blood pressure (DBP) ≥ 80 mm Hg, or
- if being treated with an antihypertensive medication at baseline or has medical history of hypertension.

Vital signs, including orthostatic vital signs, including SBP and DBP, will be measured at every visit. Descriptive statistics will summarize SBP and DBP by position (seated, supine, and standing) 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 position (seated, supine, and standing) 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 on or after the first dose of study drug or existing events that worsened after the first dose during the study and up to and including 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 to be 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 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 (defined as possibly related or probably related)
- Summary of TEAEs leading to dose discontinuation (i.e. study drug withdrawn)
- Summary of TEAEs leading to dose interruption
- 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 5.2.2)

All above summaries will be presented by PT, and by PT nested within SOC. Also, summaries by maximum severity will be provided for TEAEs and serious TEAEs.

TEAEs and serious TEAEs 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 individual patient and treatment arm, including dates of onset and resolution and associated study day, duration, serious, CTCAE grade, action taken, outcome, and relationship to study drug. Serious TEAEs 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 with the exception of HbA1c, which will be presented in % 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 to worst 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), 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, alkaline phosphatase, and gamma-glutamyl transferase (GGT), the mean and 95% CI 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 orthostatic vital signs, including systolic and diastolic BP, heart rate, respiratory rate, and body temperature, will be summarized. Descriptive statistics will be presented by position (seated, supine, and standing) for observed values as well as change from baseline for all post-baseline visits 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 Subgroup Analyses

Subgroup analyses will be performed for the primary efficacy measure (mean change from baseline in body weight) for the EE patients for the following:

- For the subgroup variable of antipsychotic medication (stratification factor).
  - Each subgroup will be analyzed as is.
  - We will perform an additional subgroup analysis by combining Aripiprazole, Quetiapine and Other.
- For the subgroup variable of disorder diagnosis (schizophrenia or bipolar disorder).
- For the subgroup variable of BMI group (30-34.9, 35-39.9, ≥ 40).

Treatment group differences will be evaluated within each category of the subgroup variable.

For all the subgroup variables, the subgroup analysis for change from baseline in body weight to each week will be conducted with MMRM. The same MMRM model as described in Section 9.8.2 will be used with terms of subgroup, subgroup-by-treatment, subgroup-by-visit, and subgroup-by-treatment-by-visit interactions added as factors. Data for non-retrieved dropouts will not be imputed. A sample of SAS code that can be used to implement the MMRM model is provided in the Section 12.2.

9.11 Other Exploratory Analyses

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

9.11.1 Responders Achieving a ≥ 7% and ≥ 10% Body Weight Loss

A responder is defined as a patient achieving ≥7% and ≥10% body weight loss, respectively, and will be determined as described in Section 9.8.3.1. Similar to the secondary efficacy endpoint, the binary responder outcome will be analyzed using a logistic regression model as described in Section 9.8.3.1.

9.11.2 Fasting Lipids

Fasting lipids (triglycerides, low-density lipoprotein [LDL], high-density lipoprotein [HDL], very low-density lipoprotein [VLDL], total cholesterol) will be summarized by visit (baseline and Week 12) using the safety population. Descriptive statistics will be presented for observed values as well as change from baseline to Week 12.

9.12 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.

9.13 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 for waist-to-hip ratio, the Protocol specifies that it may be log-transformed prior to analysis. However, the data looks reasonably symmetric, so the untransformed values will be used.

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 AE 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 or bipolar disorder 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 12;
  estimate 'Miricorilant - Placebo at Week 12'
    treat 1 -1
    treat*visit 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 -1 /cl; *Get diff
at Wk 12;
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 9.8.3.1.