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: 11 January 2022

# CLINICAL STUDY PROTOCOL CORT118335-876 (GRATITUDE)

| | |
|---|---|
| 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)** |
| Investigational Product | Miricorilant |
| Medical Monitor | [redacted] |
| Sponsor | Corcept Therapeutics Incorporated<br>149 Commonwealth Drive<br>Menlo Park, California 94025 US<br>(650) 327-3270 |
| Version | Amendment 5 |
| Date | 11 January 2022 |

## Good Clinical Practice Statement

This study will be conducted in compliance with the protocol, the International Conference on Harmonisation Good Clinical Practice guidelines, and with the ethical principles contained in the Declaration of Helsinki, or with the laws and regulations of the country in which the research is conducted, whichever provides greater protection of the human study participants. Compliance with these standards provides assurance that the rights, safety, and well-being of study participants are protected.

## Confidentiality Statement

## SPONSOR SIGNATURE PAGE

| | |
|---|---|
| Protocol Title | 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) |
| Protocol Number | CORT118335-876 |
| Version | Amendment 5 |
| Date | 11 January 2022 |

APPROVAL STATEMENT

The undersigned has reviewed the format and content of the above protocol and approved for issuance.

## PROTOCOL SYNOPSIS

| **Name of Sponsor** | **Name of Active Ingredient** | **Study Number** |
|---|---|---|
| Corcept Therapeutics | Miricorilant | CORT118335-876 |

**Title of Study**

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 Centers**

Approximately 35 sites in the US

**Phase of Development**

Phase 2

**Duration of Treatment**

Treatment duration of 12 weeks and study participation duration of ~20 weeks (up to 28 days for Screening, 12 weeks for Treatment and 4 weeks after last dose in Follow-up).

**Study Objectives**

**Safety**

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

**Primary Efficacy**

- To assess the efficacy of miricorilant compared with placebo in reversing recent antipsychotic-induced weight gain (AIWG) caused by an atypical antipsychotic medication.

**Secondary Efficacy**

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

**Pharmacokinetics**

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

**Population**

Patients with a body mass index (BMI) ≥30 kg/m$^2$ who have started any FDA-approved oral or injectable atypical antipsychotic medication (except clozapine) for the treatment of schizophrenia or bipolar disorder within the last 18 months and have since shown an increase in body weight by ≥5% within 6 months of starting the antipsychotic medication as documented by medical record, treating physician's report, or by an acceptable means of patient-documented weight gain.

**Number of Patients Planned**

Approximately 70 patients will be randomized 1:1 to receive 600 mg miricorilant or placebo in this study.

**Methodology**

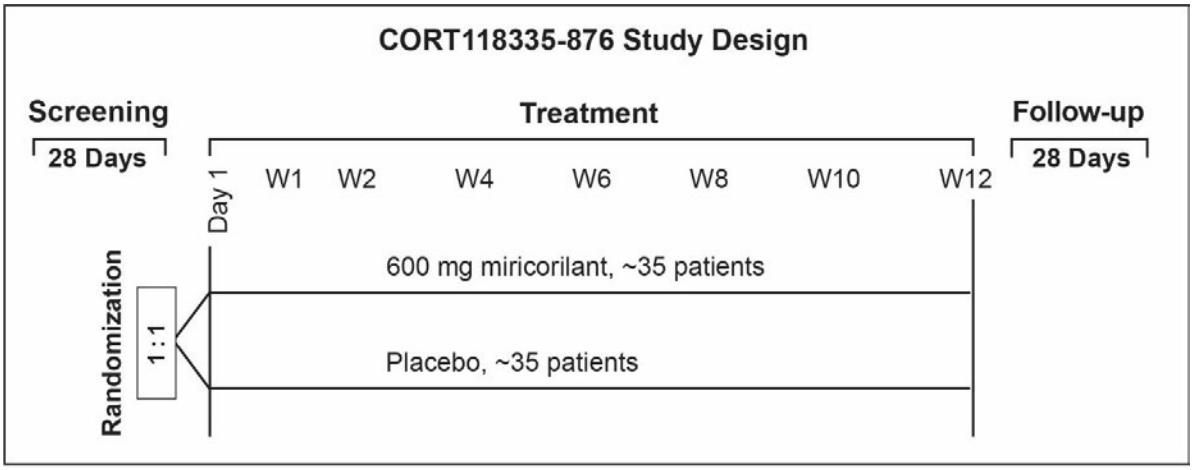
This is a randomized, double-blind, placebo-controlled study to evaluate the safety, efficacy, and PK of miricorilant in patients with schizophrenia or bipolar disorder and BMI ≥30 kg/m$^2$ who have weight gain as a result of treatment with any oral or injectable atypical antipsychotic medication (except clozapine).

The study consists of the following study periods:

- Screening Period: up to 28 days
- Treatment Period: Day 1 to Week 12
- Follow-up Period: 28 days after last study dose

The study design is shown schematically in Figure S1.

**Figure S1 Schematic of Study Design**




Abbreviation: W, Week.

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 approximately 45 patients are expected to participate. The PK substudy will be conducted at the Week 4 visit. In patients who consent to participate in the PK substudy, blood samples will be collected according to the PK plan outlined in the study manual.

**Key Inclusion Criteria**

Patients eligible for enrollment into this study must meet the following criteria:

- Are men or women ≥18 to ≤65 years old.
- Able to successfully complete placebo-tablet swallow assessment.
- Meet the criteria for schizophrenia based on medical history and the Mini International Neuropsychiatric Interview (MINI) or meet the criteria for bipolar disorder as described by the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and the MINI.
- Have started any FDA-approved oral or injectable atypical antipsychotic medication (except clozapine) for treatment of schizophrenia or bipolar disorder within 18 months of Screening. Patients with bipolar disorder will need to either be on monotherapy with an antipsychotic medication or have been on a stable dose of a mood stabilizer ≥3 months with a stable weight

and subsequently have an antipsychotic medication added that resulted in weight gain. Patients with bipolar disorder who are on a mood stabilizer must remain on a stable dose of their mood stabilizer throughout the study.

- Have shown an increase in body weight of ≥5% above their prior body weight within 6 months of atypical antipsychotic medication initiation, as documented by medical records, physician's report, or by an acceptable means of patient-documented weight gain.
  - Historical weights from medical records must be within 6 months prior to initiation of antipsychotic medication.
    - Patients who have had a treatment gap in their antipsychotic medication for ≥28 days but have restarted medication within 18 months of Screening are eligible to participate if they have documented increase in body weight of ≥5% within 6 months of restarting the antipsychotic medication. Historical weights will not be accepted for these patients.
    - Historical weights will not be accepted for patients with bipolar disorder on mood stabilizers.
  - Patients who document their own weight gain MUST show evidence of weight gain using one of the following methods: 1) using Smart Scale weight data, 2) using photographs to record weight displayed on a scale, or 3) using a weight diary.
    - Dates of weight collection need to be available for the weight gain documentation method used.
      - The scale photograph must clearly show the scale and displayed weight. The photograph must show the date and time stamp for inspection and verification by the study staff.
    - Historical "prior body weight" before the initiation of their antipsychotic medication will not be accepted for patient-documented weight.
- Have been on the same dose of oral or injectable atypical antipsychotic medication for the last month prior to Screening.
- Are clinically stable and unlikely to require change to their antipsychotic medication (i.e. medication switch or dose change) through the duration of the study (20 weeks).
- Patients with schizophrenia must have a Brief Psychiatric Rating Scale (BPRS) of ≤50 at Screening.
- Patients with bipolar disorder must have a Young Mania Rating Scale (YMRS) of ≤20 and Montgomery-Åsberg Depression Rating Scale (MADRS-SIGMA) of ≤20 at Screening.
- Have a BMI ≥30 kg/m$^2$.

**Key Exclusion Criteria**

Patients who meet any of the following exclusion criteria will not be eligible to participate in the study:

- Have psychiatric exclusion criteria:
  - An acute psychiatric condition that might require emergent intervention during the study.
  - A psychiatric hospitalization within the last 6 months prior to Screening.
  - Are currently at risk of suicide in the opinion of the Investigator or as confirmed by the following:
    - Answer "Yes" on items 4 or 5 (Columbia Suicide Severity Rating Scale [C-SSRS]-ideation) with the most recent episode occurring within the last 6 months prior to Screening.
    - Answer "Yes" to any of the 5 items (C-SSRS-behavior) with an episode occurring within the last 6 months prior to Screening.
- Have participated in another Corcept study with miricorilant.
- Are currently taking the antipsychotic medication clozapine.

- Are currently taking the mood stabilizing medication carbamazepine.
- Are currently taking more than one antipsychotic medication.
- Have poorly controlled diabetes mellitus with glycated hemoglobin (HbA1c) >10% or a fasting blood glucose >200 mg/dL.
- Have poorly controlled hypertension with a systolic blood pressure >170 mm Hg or a diastolic blood pressure >100 mm Hg by in-office blood pressure measurement.
- Have a history of symptomatic hypotension with a systolic blood pressure <100 mm Hg or a diastolic blood pressure <60 mm Hg.
- Have a recent history of orthostatic hypotension with a systolic blood pressure decrease of at least 20 mm Hg or a diastolic blood pressure decrease of at least 10 mm Hg within the last year of Screening.
- Have a history of a seizure disorder.
- Are currently using or plan to use prescription or over-the-counter weight-loss treatments during the study, including but not limited to*:
  - Olanzapine/samidorphan (Lybalvi) or other samidorphan drug combinations.
  - Prescription drugs such as orlistat (Xenical), phentermine (Adipex-P, Pro-Fast SA, Pro-Fast SR, Fastin, Oby-trim, Zantryl, Teramine, Phentride, Phentercot, Obephen, Oby-cap), phentermine/topiramate (Qsymia), liraglutide (Saxenda), semaglutide (Wegovy), or naltrexone HCl/bupropion HCl (Contrave).
  - Over-the-counter anti-obesity agents such as orlistat (Alli), herbal supplements or other alternative remedies (Cortislim, Dexatrim, Acutrim).

  *Patients currently taking these medications may participate in the study if appropriate to discontinue the medication, and if the patient is amenable to discontinuing the medication for a wash-out period of 5 half-lives prior to the baseline assessment.

  Note: Names within parenthesis are trademarks of third-party companies.
- Are currently using any prohibited medications (Section 5.4.3). Prohibited medications must be discontinued at least 5 half-lives prior to a patient receiving their first study treatment. Administration of concomitant medications (Section 5.4) are at the discretion of the Investigator and/or Medical Monitor.
- Have a history of a medical condition affecting body weight including but not limited to poorly controlled hyper- or hypothyroidism; eating disorder such as anorexia, bulimia, or binge eating; or polycystic ovary syndrome.
- Have had weight-loss surgery including, but not limited to, gastric bypass, sleeve gastrectomy, gastric band placement, or biliopancreatic diversion with duodenal switch within the last 5 years prior to Screening or are planning weight-loss surgery during the study.
- Have had liposuction within 1 year prior to Screening or have planned liposuction during the study.
- Have any elective surgery planned during the study.
- Have a clinically significant electrolyte abnormality at Screening.
- Are currently using a medication such as digoxin with an increased risk for toxicity in the event of electrolyte changes.
- Are taking an unstable dosage (change in the dose within 4 weeks prior to Screening) of a medication that may change the fluid or electrolyte status such as a diuretic.
- Have AST or ALT >3 × the upper limit of normal.

**Investigational Treatment, Dose, and Mode of Administration**

Study Drug: miricorilant 100 mg tablets

Mode of Administration: Oral administration of miricorilant tablets. Patients should take tablets with food.

Dose: 600 mg (6 × 100 mg tablets). All tablets should be taken at once and the patient should make every effort to take their miricorilant dose at the same time each day.

**Reference Product, Dose, and Mode of Administration**

Placebo tablets to match 100 mg miricorilant tablets.

Mode of Administration: Oral administration of placebo tablets. Patients should take tablets with food.

Dose: 6 placebo tablets daily. All tablets should be taken at once.

**Criteria for Evaluation**

Study endpoints corresponding to study objectives are listed below.

***Safety Endpoints***

- Incidence of adverse events (AEs), serious AEs (SAEs), and AEs leading to early discontinuation
- Changes from Baseline in clinical laboratory tests (hematology and chemistry panels) at Week 12
- Changes from Baseline in physical examinations and vital sign measurements at Week 12
- Changes from Baseline in electrocardiogram parameters at Week 12

***Primary Efficacy Endpoint***

- Change from Baseline in body weight at Week 12 for 600 mg miricorilant versus placebo

***Secondary Efficacy Endpoints***

- Percentage of patients achieving a ≥5% weight loss from Baseline at Week 12 for 600 mg miricorilant versus placebo
- Change from Baseline in waist-to-hip ratio at Week 12 for 600 mg miricorilant versus placebo
- Change from Baseline in homeostatic model assessment for insulin resistance (HOMA-IR) at Week 12 for 600 mg miricorilant versus placebo

***Exploratory Endpoints***

- The following exploratory endpoints will be analyzed:
- In all patients:
  - Change from Baseline in adrenocorticotropic hormone (ACTH) at Week 12
  - Change from Baseline in serum cortisol at Week 12
- In patients with schizophrenia
  - Changes from Baseline in BPRS, C-SSRS, and Clinical Global Impression Scale (CGI) at Week 12
- In patients with bipolar disorder
  - Changes from Baseline in C-SSRS, CGI, YMRS and the MADRS-SIGMA at Week 12
- In patients with diabetes:
  - Change from Baseline in glycated hemoglobin (HbA1c) at Week 12
  - Change in fasting blood glucose at Week 12
- In patients with high blood pressure:
  - Change from Baseline in blood pressure at Week 12

***Pharmacokinetic Endpoints***

- Key PK parameters estimated from steady-state plasma concentrations

**Statistical Methods**

***Sample Size***

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 $\alpha$=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 miricorilant 600 mg in the trial, there is a 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 (active risperidone metabolite), 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 antipsychotic medication.

***Analysis Populations***

Analysis of the safety data will be performed on the Safety Population, defined as all patients who receive at least 1 dose of study medication.

Analysis of the efficacy data will be performed on the Efficacy Evaluable (EE) Population, defined as all patients who receive ≥4 weeks of study medication and have Baseline and at least 1 body weight measurement taken on or after Week 4.

Sensitivity analyses of the primary and other key endpoints will be performed on the Intent-to-Treat (ITT) Population, defined as all patients who receive at least 1 dose of study medication.

Analysis of PK data will be performed on the PK Population, defined as all patients who have evaluable PK data.

***Safety Analyses***

An Independent Data Monitoring Committee (IDMC) will be established to conduct periodic reviews of data to ensure the safety of patients.

Adverse events will be mapped to system organ classes and preferred terms using the Medical Dictionary for Regulatory Activities. Treatment-emergent AEs will be summarized overall and displayed by system organ class and preferred term, as well as by severity, seriousness, and relationship to study treatment. Serious AEs and AEs that lead to discontinuation of study treatment or withdrawal from the study will be listed by individual patient.

Clinical laboratory test results (chemistry and hematology), vital sign measurements, physical examination findings, and ECG results will be summarized by visit using descriptive statistics. Shift tables will be constructed that describe changes from Baseline in clinical laboratory values.

***Efficacy Analyses***

The primary efficacy endpoint is the change in body weight from Baseline to Week 12. The primary endpoint will be assessed using a mixed-effect model with repeated measures (MMRM) with change in body weight at each visit as the outcome variable; baseline body weight and antipsychotic medication (stratification factor) as covariates; and randomized treatment (600 mg miricorilant or placebo), visit, and treatment-by-visit interaction as fixed effects. The difference in body weight change between miricorilant and placebo will be estimated from the model along with its 95% confidence interval (CI). The MMRM used to assess the primary endpoint will be rerun as a sensitivity analysis using the ITT Population in place of the EE Population.

The percentage of patients in each treatment group who lose ≥5% of their baseline body weight will be presented along with its 95% CI. In addition, a logistic regression model with baseline body weight and stratification factor as covariates will be used to compare miricorilant to placebo.

HOMA-IR and waist-to-hip ratio will be analyzed using similar models as the primary analysis of body weight change. Both HOMA-IR and waist-to-hip ratio may be log-transformed prior to analysis; model estimates derived from log-transformed data will be back-transformed to the original scale for presentation.

***Pharmacokinetic Analyses***

The PK data obtained from the PK substudy, including the PK parameters of miricorilant will be presented. Additionally, plasma concentrations of miricorilant will be plotted over time.

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## List of Figures

## List of Abbreviations and Definitions

| Abbreviation | Definition |
|---|---|
| ACTH | adrenocorticotropic hormone |
| AE | adverse event |
| AIWG | antipsychotic-induced weight gain |
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| ANCOVA | analysis of covariance |
| AR | androgen receptor |
| AST | aspartate aminotransferase |
| AUC | area under the concentration-time curve |
| BMI | body mass index |
| BCRP | breast cancer resistance protein |
| BPRS | Brief Psychiatric Rating Scale |
| CFR | Code of Federal Regulations |
| CGI | Clinical Global Impression |
| CI | confidence interval |
| $C_{max}$ | maximum concentration |
| C-SSRS | Columbia-Suicide Severity Rating Scale |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CYP | cytochrome P450 |
| DSM-5 | Fifth edition of the Diagnostic and Statistical Manual of Mental Disorders |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EE | efficacy evaluable |
| ET | early termination |
| FDA | (United States) Food and Drug Administration |
| FSH | follicle-stimulating hormone |
| GCP | Good Clinical Practice |
| GGT | gamma-glutamyl transferase |
| GLP | Good Laboratory Practice |
| GR | glucocorticoid receptor |
| HbA1c | glycated hemoglobin |
| hERG | human ether-á-go-go-related gene |

| Abbreviation | Definition |
|---|---|
| HIPAA | Health Information Portability and Accountability Act |
| HME | hot melt extrudate |
| HOMA-IR | homeostatic model assessment for insulin resistance |
| IB | Investigator's Brochure |
| ICF | informed consent form |
| ICH | International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IRB | Institutional Review Board |
| ITT | intent-to-treat |
| IV | intravenous |
| IWRS | interactive web response system |
| $K_i$ | inhibition constant |
| MADRS-SIGMA | Structured Interview Guide for the Montgomery-Åsberg Depression Rating Scale |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MINI | Mini International Neuropsychiatric Interview |
| MR | mineralocorticoid receptor |
| NCI | National Cancer Institute |
| NOAEL | no-observed-adverse-effect level |
| PK | pharmacokinetic(s) |
| PR | progesterone receptor |
| QTc | corrected QT interval |
| QTcF | QT interval corrected for heart rate using Fridericia's equation: $QTcF=QT/(RR^{1/3})$ |
| SAE | serious adverse event |
| SD | standard deviation |
| SDD | spray dried dispersion |
| SoA | schedule of assessments |
| T4 | thyroxine |
| TAT | tyrosine aminotransferase |
| TEAE | treatment-emergent adverse event |
| $T_{max}$ | time to maximum concentration |
| TSH | thyroid-stimulating hormone |
| UGT1A1 | uridine diphosphate glucuronosyltransferase 1A1 |
| US | United States |

| Abbreviation | Definition |
|---|---|
| WBC | white blood cell (count) |
| YMRS | Young Mania Rating Scale |

# 1 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

## 1.1 Therapeutic Area

Antipsychotic-induced weight gain (AIWG) is the condition in which patients with schizophrenia, bipolar disorder, or other conditions treated with antipsychotic medications gain weight.

There are currently no approved treatments for AIWG; adjunctive pharmacological treatment, behavioral therapy, and antipsychotic medication switch have limited efficacy (Maayan et al. 2010, Mukundan et al. 2010, Mizuno et al. 2014). Dietary counseling and exercise programs have shown only modest effects on weight in these patients (Dayabandara et al. 2017). The investigational product miricorilant (CORT118335) has shown efficacy in rat models of AIWG and is expected to provide benefit in patients with AIWG.

### 1.1.1 Background

Atypical antipsychotic medications were initially developed to address the extrapyramidal effects and tardive dyskinesia seen with first-generation antipsychotic medications. These medications, while efficacious, cause significantly more weight gain in patients than the first-generation medications. Though all antipsychotic medications cause some amount of weight gain, the atypical antipsychotics (clozapine and olanzapine, followed by risperidone and quetiapine) appear to cause the most weight gain (ADA/APA/AACE/NAASO 2004). Olanzapine and clozapine cause between 4.0 to 4.5 kg of weight gain on a standard dose over the course of 10 weeks (Allison and Casey 2001). Weight gain is of concern in the background of increasing rates of obesity and diabetes among the general population, since both are risk factors for cardiovascular disease.

In addition to weight gain, antipsychotic medications also increase insulin resistance, cholesterol, and serum triglycerides, significantly increasing cardiovascular risk in this patient population (Dayabandara et al. 2017). Patients with schizophrenia treated with antipsychotics have increased risk of mortality (2–3 times above that of the general population), which corresponds to a 10 to 25 year reduction in life expectancy, largely due to increased cardiovascular disease (Laursen et al. 2012). In patients with bipolar disorder as well, treatment with atypical antipsychotic medications such as olanzapine, clozapine, quetiapine, and risperidone is associated with weight gain (McIntyre et al. 2003, Narasimhan et al. 2007, Torrent et al. 2008, Nashed et al. 2011). The weight gain can exacerbate other associated health risks such as compromised neurocognitive function or can increase obesity-related metabolic disorders in this patient population (McIntyre et al. 2003, Nashed et al. 2011). Weight gain in patients with schizophrenia or bipolar disorder is also associated with discontinuation of antipsychotic medications (Liebermann et al. 2005; Torrent et al. 2008), which could lead to a decrease in their overall effectiveness.

### 1.1.2 Therapeutic Hypothesis

The pathogenesis of weight gain from taking antipsychotic medications is not well understood. Antipsychotic medications act on a multiple neuroreceptors and may increase appetite and

decrease energy expenditure (Gothelf et al. 2002, Graham et al. 2005). Dysregulation of the hypothalamic-pituitary-adrenal axis has been implicated with the use of atypical antipsychotics. Rats treated with clozapine showed an increase in corticosterone (Tulipano et al. 2007).

A role for the glucocorticoid receptor (GR) has been suggested in AIWG. In healthy volunteers treated with olanzapine or risperidone, mifepristone, a GR antagonist, ameliorated weight gain associated with the antipsychotic medication (Gross et al. 2009, Gross et al. 2010). Miricorilant, which is a mixed agonist/antagonist of the GR and an antagonist of the mineralocorticoid receptor (MR) has shown to be effective in a rat model of AIWG (Hunt et al. 2012).

## 1.2 Miricorilant: A Mixed Agonist/Antagonist of the Glucocorticoid-Receptor and Antagonist of the Mineralocorticoid-Receptor

Miricorilant is a new molecular entity that is a mixed agonist/antagonist of the GR and an antagonist of the MR, and is being developed for the treatment of AIWG. The goals of this study (CORT118335-876 [GRATITUDE]) are to evaluate the safety, efficacy, and pharmacokinetics (PK) of miricorilant in reversing AIWG in patients taking any FDA-approved oral or injectable atypical antipsychotic medication (except clozapine) for the management of schizophrenia or bipolar disorder.

Detailed information about miricorilant is provided in the Investigator's Brochure (IB). This section summarizes the key data that are relevant to this study.

### 1.2.1 Nonclinical Summary

#### 1.2.1.1 Pharmacology

This section summarizes in vitro and in vivo data relating to the pharmacology of miricorilant as a mixed agonist/antagonist of the GR. In most models, mifepristone was used as an active comparator. Mifepristone is an antagonist of the progesterone receptor (PR), androgen receptor (AR), and GR. Miricorilant has similar GR antagonism without effects at the PR or AR.

##### 1.2.1.1.1 In Vitro Pharmacology

Miricorilant is a high-affinity mixed agonist/antagonist of cortisol at the GR. In a fluorescence polarization ligand-binding assay to assess affinity for GR, miricorilant had a $K_i$ of 0.5 nM. Functional antagonism was assessed by measuring the ability of miricorilant to prevent a dexamethasone-induced increase in the activity of tyrosine aminotransferase (TAT). The expression of the TAT gene is regulated by GR, and a GR agonist such as dexamethasone increases gene expression, protein production, and enzyme activity. For routine screening, the human liver carcinoma cell line Hep-G2 and the rat hepatoma cell line H4-II-EC4 were used. Miricorilant is a full antagonist in the human Hep-G2 cell line, with no evidence of agonist activity, but does not achieve complete antagonism in the rat H4-II-EC4 cell line. When tested in the absence of dexamethasone, miricorilant acted as partial agonist in the rat cell line. In a reporter gene assay that assessed the ability of miricorilant to inhibit the dexamethasone-induced increase in luciferase expression, miricorilant behaved as a full antagonist, with a $K_i$ of 24 nM (Hunt et al. 2012). GR antagonism was assessed using a protein:protein interaction assay, which

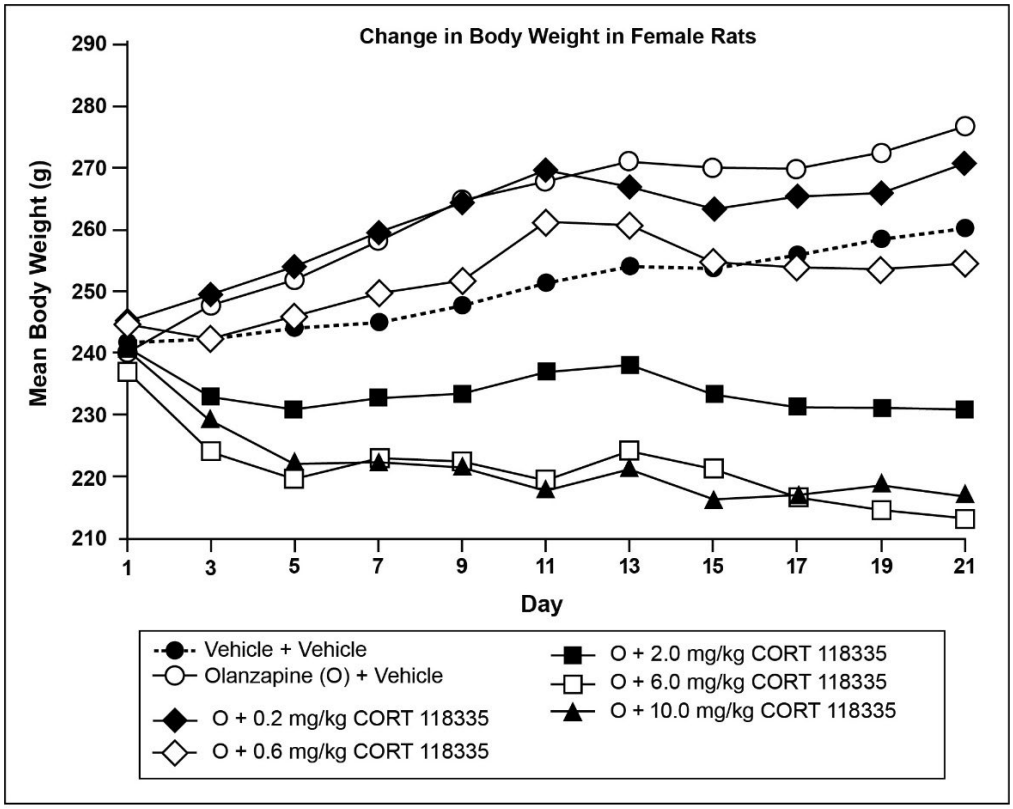
assesses activation of a nuclear hormone receptor by measuring the interaction of a full-length nuclear hormone receptor with a nuclear fusion protein, and miricorilant had a $K_i$ of 118 nM.

#### 1.2.1.1.2 In Vivo Pharmacology

Three studies (MPI 950-033, MPI 950-034, and MPI 950-035) have been conducted to evaluate the ability of miricorilant, at various doses, to prevent weight gain in female rats (10 per group) administered the antipsychotic medication olanzapine and fed a normal diet. The most commonly used animal model of antipsychotic-induced weight gain involves the administration of olanzapine to female rats. Several authors have reported differential effects of olanzapine depending on the diet used, the route, frequency and duration of drug administration, and the sex of the animals (reviewed in Van der Zwaal 2014). Olanzapine leads to a robust and reproducible increase in body weight in female rats, but results in male rats are less reliable. Thus, female rats were used in the studies reported here. In all 3 studies, olanzapine was administered by oral gavage at a dose of 1.2 mg/kg twice a day, 12 hours apart (i.e., 2.4 mg/kg/day, for 21 consecutive days). This series of studies shows a dose-dependent ability of miricorilant to prevent olanzapine-induced increases in body weight, food consumption, and abdominal fat content in female rats (Miricorilant IB).

Of these 3 studies, MPI 950-035 (Hunt et al. 2012) investigated the lowest doses of miricorilant. At doses above 2 mg/kg/day in combination with olanzapine, or 0.6 mg/kg/day alone, miricorilant reduced basal body weight (Figure 1).

**Figure 1 Effect of Miricorilant (CORT118335) on Body Weight in Female Rats Given Olanzapine**

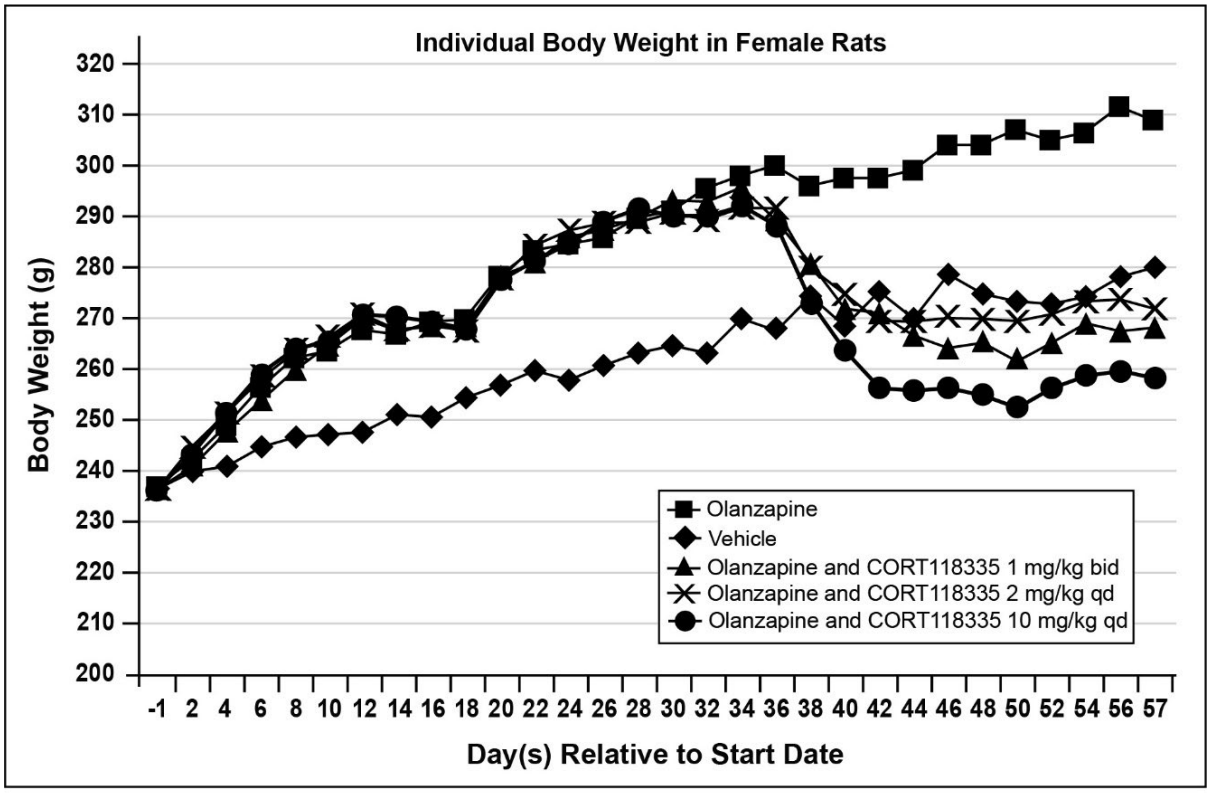



Source: Hunt 2012
Abbreviation: O, olanzapine.

The ability of miricorilant to reverse (rather than prevent) olanzapine-induced weight gain in female rats was investigated in 3 separate studies. In the first study (MPI 950-144) rats were fed a normal diet and administered olanzapine at a dose of 1.2 mg/kg twice a day, (i.e., 2.4 mg/kg/day, for 56 consecutive days). A control group (n=12), that received only vehicle throughout the duration of the study, was also included.

A statistically significant increase in body weight was observed in all rats treated with olanzapine during the induction phase, and this effect was maintained for the duration of the study in rats that received only vehicle in the treatment phase (Figure 2). Miricorilant at all doses completely abrogated the olanzapine-induced increase in body weight gain and food consumption. The effects noted with a total daily dose of 2 mg/kg, regardless of whether this was administered as a single dose of 2 mg/kg (noted below as Mid Dose QD) or a split dose of 1 mg/kg twice a day (noted below as Low Dose BID), were very similar. Effects were observed from the first week of dosing and then throughout the remainder of the study.

**Figure 2 Reversal of Olanzapine-Induced Weight Gain in Female Rats**




Source: MPI 950-144
Olanzapine: 2.4 mg/kg/day; CORT118335 Low Dose=1 mg/kg; CORT118335 Mid Dose=2 mg/kg; CORT118335 High Dose=10 mg/kg

The administration of olanzapine to female rats fed a high-fat diet results in a rapid increase in body weight, with a statistically significant effect noted by Day 5. The ability of miricorilant to reverse the effects of olanzapine in this model has been investigated in two studies (RenaSci RS1738 and RS1854), and doses as low as 0.5 mg/kg/day fully reverse the effects of olanzapine. These results provide additional support for the potential utility of miricorilant in the treatment of AIWG in patients.

### 1.2.2 Absorption, Distribution, Metabolism, and Elimination

The plasma protein binding of miricorilant in rat and human was >99.9% (Corcept PK-118335-008) and in mouse and monkey was >99% (Corcept PK-118335-013).

In vitro studies with human cytochrome P450 (CYP) isoforms indicated that miricorilant was metabolized almost exclusively by CYP2C19 (94%) (Corcept PK-118335-012). Miricorilant also exhibited inhibitory potential of CYP3A4, CYP2C8, CYP2C9, uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), and breast cancer resistance protein (BCRP) in vitro (Corcept PK-118335-004, Corcept PK-118335-009, and Sygnature Discovery TPT-125281-118335-002).

Fecal elimination represented the principal route of elimination with 98.7% ± 2.48% recovered.

### 1.2.3 Safety Pharmacology and Toxicology

The nonclinical safety of miricorilant has been evaluated in preliminary ascending single- and repeat-dose studies followed by Good Laboratory Practice (GLP) 28-day and 91-day repeat-dose toxicology studies in mice and monkeys. Dose range finding reproductive toxicology studies have been conducted in mice and rabbits. In addition, standard packages of GLP safety pharmacology studies (*in vitro* human ether-à-go-go related gene [hERG] assay, cardiovascular effects in monkeys, respiratory function in mice, and neurobehavioral effects in mice) and genotoxicity studies (*in vitro* bacterial and mammalian cell assays; *in vivo* assay in mice), have been completed. All safety pharmacology and toxicology studies used oral administration, the intended clinical route. Miricorilant was not genotoxic in any study. There were no adverse findings in any safety pharmacology study up to the highest dose studied (500 mg/kg in mice, 400 mg/kg in monkeys). In the GLP hERG assay, 0.9 μM miricorilant (the highest concentration studied, limited by solubility) produced maximum inhibition of hERG-mediated potassium currents of 23.8%.

Mouse and monkey 28- and 91-day general GLP toxicology studies have been completed with miricorilant as follows:

- Mice were administered doses of 30, 100, 300, or 500 mg/kg daily by oral gavage for 28 days. No adverse effects were observed at any dose in this study, therefore the no observed adverse effect level (NOAEL) was 500 mg/kg. The NOAEL was associated with a Day 28 miricorilant area under the curve $(AUC)_{0\text{-}24}$ of 36,184 ng·h/mL in male mice and 36,896 ng·h/mL in female mice (MPI 950-126).
- Monkeys were administered doses of 20, 100, or 400 mg/kg daily by oral gavage for 28 days. No adverse effects were observed at any dose in this study, so the NOAEL was 400 mg/kg. The NOAEL was associated with a Day 28 miricorilant $AUC_{0\text{-}24}$ of 9,006 ng·h/mL in male monkeys and 7,030 ng·h/mL in female monkeys (MPI 950-127).
- Mice were administered doses of 30, 100, or 500 mg/kg daily by oral gavage for 91 days. No adverse effects were observed at any dose in the study and the NOAEL was considered to be 500 mg/kg. The NOAEL was associated with a Day 91 $AUC_{0\text{-}24}$ of 34,230 ng·h/mL in male mice and 37,950 ng·h/mL in female mice (MPI 950-140).
- Monkeys were administered doses of 20, 50, or 200 mg/kg daily by oral gavage for 91 days. No adverse effects were noted in female monkeys, and the NOAEL was 200 mg/kg, which was associated with an $AUC_{0\text{-}24}$ of 30,145 ng·h/mL on Day 1 and an $AUC_{0\text{-}24}$ of 19,465 ng·h/mL on Day 91. In male monkeys, the NOAEL was 50 mg/kg since adverse clinical effects, specifically abnormal feces, decreased activity, lack of appetite, hunched posture, dehydration and ataxia, were noted at the highest dose. The NOAEL was associated with a Day 1 $AUC_{0\text{-}24}$ of 19,937 ng·h/mL and a Day 91 $AUC_{0\text{-}24}$ of 3,813 ng·h/mL (MPI 950-139).

Other treatment-related findings in the nonclinical studies are considered related to the mode of action of miricorilant as a GR and MR antagonist. Although the risk of clinically significant safety concerns is considered to be low, potential adverse effects of miricorilant, based on the pharmacological effect of GR antagonists, may include signs and symptoms consistent with

excessive GR antagonism (e.g., weakness, tiredness, dizziness, orthostatic hypotension, hypoglycemia, dehydration, nausea, vomiting, diarrhea, and muscle aches). Potential adverse events of miricorilant, based on the pharmacological effects of an MR antagonist, may include signs and symptoms of excessive MR antagonism (e.g., hyperkalemia or hypotension).

Reproductive toxicity studies have been completed in mice and rabbits as follows:

- In the preliminary dose range finding study in mice, miricorilant was administered daily by oral gavage from gestation day (GD) 6 through 15 at doses of 0 (vehicle), 10, 30, 100 and 300 mg/kg/day. No test article-related effects were observed on maternal survival, clinical observations, or maternal macroscopic evaluations at necropsy. No effects of miricorilant were observed on fetal sex ratios or fetal body weights. Test article-related maternal effects were observed at all dose levels evaluated. Test article-related fetal external malformations of cleft palate were observed at all dose levels evaluated. Additionally, the malformation exencephaly was observed in 2 fetuses in 1 litter at the 100 mg/kg/day dose. The relationship of this finding to miricorilant is unclear.
- In the preliminary dose range finding study in rabbits, miricorilant was administered daily by oral gavage from GD 7 through 19 at doses of 0 (vehicle), 3, 10, 30 and 100 mg/kg/day. No clear miricorilant-related effects were observed on maternal survival, food consumption, maternal macroscopic observations, or number of corpora lutea at any of the dose levels evaluated. Miricorilant-related maternal effects were observed at doses ≥10 mg/kg/day in this study. No effects of miricorilant were observed on fetal external evaluations at 3 and 10 mg/kg/day. Miricorilant related effects at doses above 10 mg/kg/day included adverse pregnancy outcomes, such as abortions.

Preliminary non-GLP prenatal development studies conducted in mice and rabbits suggest that miricorilant should not be administered to pregnant women due to adverse effects on fetal development (mice) or adverse pregnancy outcomes (rabbits).

Women of childbearing potential and men with partners of childbearing potential in clinical studies must use a highly efficacious form of birth control as outlined in Section 4.1.

More information is provided in the current Miricorilant IB.

## 1.3 Clinical Summary

Clinical experience in humans with miricorilant is derived from four Phase 1 studies conducted in healthy adult subjects (Studies CORT118335-850, CORT118335-851, CORT118335-852, and CORT118335-853):

Available safety and PK data from these studies are presented in this section.

### 1.3.1 Phase 1 Study CORT118335-850

CORT118335-850, the first-in-human study of miricorilant, was an adaptive-dose, single-ascending dose (SAD) and multiple-ascending dose (MAD) study of the safety, tolerability, PK, and food/pharmacological effects of orally administered miricorilant in male and female healthy subjects.

Drug product was administered as a hot melt extrudate (HME) capsule, a suspension of spray-dried dispersion (SDD) with vehicle in bottle, or as a 100 or 300 mg tablet. The HME

capsule and 300 mg tablet led to lower than expected miricorilant exposures and will not be evaluated further in clinical development. Thus, only the efficacy, safety, and PK results of the suspension (SDD) and 100 mg tablet formulations are summarized below.

In the SAD portion of the study, miricorilant was administered under fasting conditions as 100, 300, 900, or 1500 mg. The SAD suspension portion of the study also evaluated 900 mg miricorilant administered under fed conditions with a high-fat breakfast versus 900 mg miricorilant administered under fasting conditions.

In the MAD dose portion of the study, miricorilant was administered once-daily under fasting conditions for 14 days as 150, 450, or 900 mg in suspension.

In addition, 2 × 100 mg miricorilant tablets and 2 × 300 mg miricorilant tablets were evaluated under fasting and fed conditions.

**Safety Results**

*Drug-Related Treatment-Emergent Adverse Events*

Across all SAD/suspension cohorts, 1 of 7 (14.3%) fasted and 1 of 1 (100%) fed placebo subjects reported one or more TEAEs. Of subjects treated with miricorilant, the proportion reporting at least 1 TEAE ranged from 0 to 60% across all doses. No trend in the proportion reporting TEAEs with dose was apparent. In the MAD/suspension part of the study, 4 of 8 (50.0%) placebo treated subjects reported at least 1 TEAE. Across all doses of miricorilant, 3 of 8; 33.3% (150 mg and 450 mg) or 3 of 9; 37.5% (900 mg) subjects reported at least 1 TEAE. In the food-effect (FE)/suspension part of the study, 3 subjects reported 4 TEAEs, none of which were considered related to treatment.

*Serious Adverse Events*

One serious adverse event (SAE) was reported in Study CORT118335-850. One subject experienced a non-fatal, acute myocardial infarction 28 days after a single oral dose of miricorilant 300 mg in suspension. The event was not considered related to study drug, but more likely related to the subject's underlying coronary artery disease.

No deaths were reported during the study.

*Adverse Events Leading to Discontinuation*

No AEs leading to discontinuation were reported.

*Vital Signs, Laboratory Evaluations, and Physical Examinations*

There were no clinically significant findings in any of the vital signs or laboratory evaluations. During physical examinations, a mild cardiac murmur was observed at the follow-up examination in a subject who had been treated with a single dose of miricorilant 900 mg in suspension under both fasted and fed conditions. The finding was not noted on previous examinations; the Investigator considered this asymptomatic finding most likely to be a pre-existing condition and not related to study drug.

*12-Lead Electrocardiogram*

Electrocardiograms (ECGs) were obtained in triplicate in the MAD/suspension parts of the study. Single ECGs were obtained in the SAD/suspension and FE/suspension parts of the study

unless abnormalities were detected. No subject recorded QT interval corrected for heart rate using Fridericia's equation (QTcF) intervals that were >450 msec at any time point and no subject had increases in QTcF interval from baseline that were >30 msec.

*Holter Electrocardiogram: Exposure-Response Analysis*

In Study CORT118335-850, across the wide range of miricorilant doses/exposures evaluated, the majority of subjects recorded mean QTcF intervals that were ≤450 msec at all time points; those that did not were only slightly outside this range, with none exceeding 500 msec and none reported as clinically significant. Based on the totality of data, miricorilant does not have a clinically relevant effect on the QTc interval.

**Pharmacokinetic Results**

Plasma concentrations of miricorilant increased in an approximately dose-proportional manner following single-dose administration of 100 to 900 mg under fasting conditions, and in less than dose-proportional increases for doses of 900 or 1500 mg of the SDD-suspension formulation. Based on the concentration-time profile following administration of single 100 or 300 mg doses, the terminal half-life of miricorilant was estimated to be approximately 21 to 23 hours. Administration of 900 mg miricorilant suspension under fed conditions (with a high-fat breakfast) resulted in substantial increases in plasma concentrations versus fasting administration, with geometric mean (coefficient of variation [CV%]) relative bioavailability values (fed versus fasting) of 245% (24.5%) based on the maximum concentration ($C_{max}$) and 345% (28.8%) based on $C_{max}$ and $AUC_{0\text{-}inf}$.

In the MAD portion of the study, following once-daily administration of miricorilant suspension under fasting conditions for 14 days, the plasma concentrations of miricorilant increased in an approximately dose-proportional manner. The overall accumulation ratio ($AUC_{0\text{-}tau}$) were 2.17 for the 150 mg dose, 1.81 for the 450 mg dose, and 2.40 for the 900 mg dose.

Following a single oral administration of 200 mg miricorilant (2 × 100 mg tablet) in the fasted state, the mean miricorilant $C_{max}$, $AUC_{24}$, and $AUC_{inf}$ were 105 ng/mL, 996 ng·h/mL, and 1790 ng·h/mL respectively. These were contained within the exposures observed following the 100 and 300 mg miricorilant doses. Based on the previously observed Part 4 (SAD/suspension) PK data, and the dose-proportional increases in miricorilant exposures to 900 mg (suspension), the exposures of 200 mg miricorilant (fasted), was modestly lower than expected. The geometric mean $C_{max}$ of 105 ng/mL for 200 mg miricorilant (2 × 100 mg tablets) is approximately 25% lower versus predicted $C_{max}$ of 140 ng/mL based on dose-proportionality.

Following administration of 200 mg miricorilant (2 × 100 mg tablets) under fed conditions (with a high-fat breakfast), miricorilant $C_{max}$, $AUC_{last}$ and $AUC_{inf}$ increased by 1.8-, 2.2- and 2.1-fold, respectively, compared to 200 mg miricorilant administered under fasting conditions.

**Efficacy Results**

This study was designed to evaluate safety and PK and was not powered to detect efficacy. There was no notable difference between miricorilant- and placebo-treated subjects in mean change from baseline in body weight, and no clinically significant individual laboratory values.

### 1.3.2 Phase 1 Study CORT118335-851

CORT118335-851 was an open-label study conducted with [$^{14}$C]-miricorilant to assess the absolute bioavailability (Part 1) and the mass balance recovery, absorption, metabolism and elimination, and metabolite profile and identification (Part 2) of miricorilant in healthy male subjects.

Subjects were healthy men, aged 18 to 65 years (Part 1) and 30 to 65 years (Part 2), with a body mass index (BMI) in the range of 18.0 to 30.0 kg/m$^2$. In Part 1, 6 subjects received a single oral dose of 900 mg miricorilant in suspension followed by a microdose (100 µg) of [$^{14}$C]-miricorilant containing a microtracer amount of $^{14}$C given as an intravenous infusion. In Part 2, 6 subjects received a single oral dose of 150 mg [$^{14}$C]-miricorilant oral solution in caprylic acid.

**Safety results**

*Drug-Related Treatment-Related Adverse Events*

No TEAEs were reported in Part 1 of the study. In Part 2 of the study, 5 of 6 subjects reported at least 1 TEAE; only 1 TEAE (upper abdominal pain) was considered possibly related to miricorilant.

*Serious Adverse Events*

No SAEs were reported in Study CORT118335-851.

*Adverse Events Leading to Discontinuation*

No AEs leading to discontinuation were reported in Study CORT118335-851.

**Pharmacokinetic Results**

PK analysis in Part 1 (absolute bioavailability) was performed in 6 subjects who received a single oral dose of 900 mg miricorilant in suspension under fasting conditions and a microdose of 100 µg miricorilant containing a [$^{14}$C] microtracer by intravenous infusion. The geometric mean absolute bioavailability of miricorilant was determined to be 16.9%.

PK analysis in Part 2 (mass balance) was performed in 6 subjects who received a single oral administration of 150 mg [$^{14}$C]-miricorilant as a solution in caprylic acid (5 mL) under fed conditions. (Note: Exposure with this formulation was higher than that observed in Study CORT118335-850 for the same dose of the suspension). Following administration of this single oral dose of 150 mg [$^{14}$C]-miricorilant, total [$^{14}$C]-radioactivity was quantifiable in whole blood in all subjects for 2–12 hours and remained so for 12–24 hours postdose. Plasma concentrations of total radioactivity were evident for 1–4 hours postdose. Maximum plasma concentrations occurred 2–12 hours postdose. Concentrations then declined in a biphasic manner and remained quantifiable for between 24 and 48 hours postdose. In comparison with the total [$^{14}$C]-radioactivity observed in plasma, the total [$^{14}$C]-radioactivity observed in whole blood was lower at all time points where radioactive levels were detectable. The whole blood:plasma concentration ratio based on total [$^{14}$C]-radioactivity ranged from 0.613–0.763. Administration of a single oral dose of 150 mg [$^{14}$C]-miricorilant resulted in the majority of total radioactivity being recovered in the feces (mean, 89.1%), with much lower amounts (mean, 4.6%) in the urine. These results suggest that the predominant route of elimination is hepatic.

### 1.3.3 Phase 1 Study CORT118335-852

CORT118335-852 is a two-part, single-center, double-blind, randomized, placebo-controlled assessment of the effect of the miricorilant, 100 mg tablets (as 600 mg [6 × 100 mg tablets] and 900 mg [9 × 100 mg tablets given as a divided dose]) on weight gain induced by multiple doses of 10 mg olanzapine in healthy male subjects.

In Part 1, 66 subjects received 10 mg daily of olanzapine for 14 days and were randomized in a 1:1 ratio to receive 600 mg of miricorilant tablets daily or placebo. Part 1 is complete and final unblinded data are available. In Part 2, 30 subjects received 10 mg daily of olanzapine for 14 days and were randomized in a 4:1 ratio to receive 900 mg of miricorilant tablets daily (600 mg in the morning and 300 mg in the evening) or placebo. Part 2 is complete and final unblinded data are available.

**Safety Results**

No deaths or SAEs were reported in this study.

All subjects participating reported at least 1 TEAE. The majority of these TEAEs were attributed by the Investigator to the coadministered olanzapine (122 of the 150 TEAEs in the pooled placebo group, 85 of the 109 TEAEs in the 600 mg miricorilant group, and 53 of the 74 TEAEs in the 900 mg group). Only one subject had a severe TEAE in the placebo group of Part 1 (described below); the majority of TEAEs reported were mild.

In Part 1, 6 subjects were withdrawn early due to moderate or severe elevations in aminotransferases: 1 subject was administered miricorilant and olanzapine (1 moderate elevation) and 5 subjects were administered with placebo and olanzapine (1 severe and 4 moderate elevations).

Two subjects in Part 2 of the Study were withdrawn early due to moderate elevations in aminotransferases: 1 subject was administered with miricorilant and olanzapine and the other subject was administered with placebo and olanzapine.

All TEAEs of elevated aminotransferases resolved following discontinuation of treatment; none had features of drug-induced liver injury (DILI) and subjects were asymptomatic.

**Efficacy Results**

In Part 1, healthy subjects administered olanzapine plus 600 mg of miricorilant gained less weight than subjects receiving olanzapine plus placebo. In addition, markers of liver damage that often rise temporarily at the start of olanzapine therapy increased less sharply in subjects receiving miricorilant, suggesting that miricorilant may have protective effects in the liver.

Part 2 confirmed the weight mitigation results of Part 1. In Part 2, subjects treated with miricorilant showed statistically significantly smaller increases in triglycerides than the placebo group.

**Pharmacokinetic Results**

In Part 1, following once daily administration of miricorilant, 100 mg tablets at a total daily dose of 600 mg (6 × 100 mg tablets QAM only), the geometric mean (geometric CV%) $AUC_{0\text{-}24}$, $C_{max}$, and $C_{24}$ were 6,680 (46.9) ng·h/mL, 494 (40.6) ng/mL, and 153 (67.4) ng/mL, respectively.

In Part 2, following twice daily administration of miricorilant, 100 mg tablets at a total daily dose of 900 mg (6 × 100 mg tablets QAM plus 3 × 100 mg tablets QPM), the geometric mean (geometric CV%) $AUC_{0-24}$, $C_{max}$, and $C_{24}$ were 17000 (41.9) ng·h/mL, 958 (38.4) ng/mL, and 547 (56.4) ng/mL, respectively.

### 1.3.4 Phase 1 Study CORT118335-853

This is an ongoing Phase 1, single-center, randomized, single-and multiple-dose study to assess the safety, tolerability, and PK of the miricorilant,150 mg tablet formulation proposed for use in future Phase 2 studies.

**Safety Results**

As of June 25, 2020, no deaths or SAEs have been reported in this ongoing study.

**Pharmacokinetic Results:**

In Cohort 1 (n=6) and cohort 2 (n=9), miricorilant tablets were administered, under fed conditions, as a single oral dose of 300 mg (2 × 150 mg tablets) or 900 mg (6 × 150 mg tablets), respectively. Preliminary PK data from both cohorts indicate that administration of the miricorilant tablet, 150 mg tablet under fed conditions provides generally similar miricorilant exposures as the miricorilant, 100 mg tablet under fed conditions (data from Study CORT118335-850), on a dose normalized basis.

## 1.4 Rationale for Study Design and Dose Regimen

Antipsychotic-induced weight gain is the condition in which patients taking antipsychotic medications gain weight. As a result, patients are at increased risk for cardiovascular morbidity and mortality thought to be related to the increased incidence of metabolic syndrome. Approximately half of patients who take antipsychotic medications are obese (Annamalai 2017). There are currently no approved treatments for AIWG, and adjunct pharmacological treatment, behavioral therapy, and antipsychotic medication switch have limited efficacy. Miricorilant has shown efficacy in rat models of AIWG and is expected to provide benefit in patients with AIWG. This study is being conducted because GR antagonism has previously been shown to prevent weight gain in healthy volunteers taking olanzapine or risperidone (Gross et al. 2009, Gross et al. 2010).

### 1.4.1 Differences Statement

This is the first Phase 2 study with miricorilant to evaluate its ability to treat AIWG caused by any oral or injectable atypical antipsychotic medication (except clozapine) in obese patients with schizophrenia or bipolar disorder who have recently gained weight. Patients will have been on their antipsychotic medication for 18 months or less and have demonstrated weight gain within 6 months of starting the antipsychotic medication.

### 1.4.2 Design Considerations

This is a Phase 2, randomized, double-blind, placebo-controlled study to evaluate the safety, efficacy, and PK of miricorilant. This study will be conducted in the USA, at approximately 35 sites, and will randomize approximately 70 patients with schizophrenia or bipolar disorder

who have recent AIWG (see Section 4.1, exclusion criterion #6) in a 1:1 ratio to 600 mg miricorilant or placebo.

The study will consist of 4 weeks of screening, 12 weeks of treatment, and 4 weeks of follow-up. Routine assessments of safety will consist of AE monitoring, measurement of vital signs, recording 12-lead ECG, physical examination, and clinical laboratory safety tests. Samples will be collected to determine standard PK parameters for miricorilant for patients who participate in the PK substudy.

### 1.4.3 Rationale for Dose Selection and Regimen

Single doses of miricorilant have been well tolerated up to doses of 2700 mg and multiple doses have been well tolerated up to 900 mg daily for 14 days. The dose chosen for this study are based on results from nonclinical studies in rats, in which miricorilant showed reversal of weight gained while on olanzapine (MPI 950-033, MPI 950-034, and MPI 950-035). In a Phase 1, placebo-controlled study in healthy volunteers, miricorilant administered at 600 mg once daily for 14 days demonstrated efficacy in mitigating olanzapine-induced weight gain (Study CORT118335-852, summarized in Section 1.3.3). CORT118335-876 is designed to evaluate the safety, efficacy, and PK of miricorilant to treat recent AIWG in patients with schizophrenia or bipolar disorder with the same lower dose (600 mg) of miricorilant used in Study CORT118335-852.

### 1.4.4 Rationale for Study Design

This is the first study with miricorilant in obese patients with AIWG. Miricorilant, which is a mixed agonist/antagonist of the GR and an antagonist of the MR, has been shown to be effective in a rat model of AIWG (Hunt et al. 2012) and there is evidence that suggests GR antagonism may alleviate AIWG. In healthy volunteers treated with olanzapine or risperidone, mifepristone (a GR antagonist) ameliorated weight gain associated with the antipsychotic medication (Gross et al. 2009, Gross et al. 2010). The current study is powered to compare miricorilant and placebo, to determine whether once daily dosing of miricorilant for 12 weeks results in improvement of weight gain in patients with schizophrenia or bipolar disorder who are taking any FDA-approved oral or injectable atypical antipsychotic medication (except clozapine) for the management of schizophrenia or bipolar disorder.

This study is placebo controlled to account for the effects of trial participation, and patients will be randomized to treatment or placebo in a double-blind manner to reduce bias. Miricorilant will be compared to placebo for safety, efficacy, and PK results.

## 1.5 Benefits and Risks

Miricorilant has shown efficacy in rat models of AIWG and is expected to provide benefit in patients with AIWG. Weight gain is especially of concern in the background of increasing rates of obesity and diabetes among the general population, both risk factors for cardiovascular disease and early death. Patients with schizophrenia have an increased risk of mortality 2 to 3 times above that of the general population, which corresponds to a 10–25-year reduction in life expectancy, largely due to increased cardiovascular disease (Laursen et al. 2012). In patients with bipolar disorder as well, treatment with atypical antipsychotic medications such as

olanzapine, clozapine, quetiapine, and risperidone is associated with weight gain (McIntyre et al. 2003, Narasimhan et al. 2007, Torrent et al. 2008, Nashed et al. 2011). The weight gain can exacerbate other associated health risks such as compromised neurocognitive function or can increase obesity-related metabolic disorders in this patient population (McIntyre et al. 2003, Nashed et al. 2011). Reversal or possibly prevention of AIWG is expected to provide a clinically meaningful improvement in general health outcomes and life expectancy in this population.

Based on the totality of data for miricorilant, the potential for clinically relevant drug-drug interactions in this study is minimal. In general, the class of atypical antipsychotic medications has the potential to undergo drug-drug interactions that are mediated predominately by CYP1A2, CYP2D6, and/or CYP3A4. Importantly, miricorilant does not affect the activity of CYP1A2 and CYP2D6, and in vitro data indicate that any inhibitory effect of miricorilant on CYP3A4 in vivo would be expected to be only weak-to-moderate (Corcept PK-118335-004). Additionally, there is no evidence that GR antagonism interferes with the efficacy of antipsychotic medications.

The potential for drug-drug interactions between miricorilant and mood stabilizer medications is minimal, except for carbamazepine. In general, mood stabilizer medications are not expected to affect the activity of CYP2C19, the enzyme primarily responsible for the elimination of miricorilant. Furthermore, mood stabilizer medications are primarily eliminated renally and/or are glucuronidated; only carbamazepine is primarily metabolized by CYP3A4, for which miricorilant has shown inhibitory potential in vitro.

Potential adverse effects of miricorilant may include signs and symptoms consistent with excessive GR antagonism (e.g., weakness, tiredness, dizziness, orthostatic hypotension, hypoglycemia, dehydration, nausea, vomiting, diarrhea, and muscle aches) and excessive mineralocorticoid receptor (MR) antagonism (e.g., hyperkalemia and hypotension).

Many atypical antipsychotic medications have both orthostatic hypotension and drug induced leukopenia/neutropenia as reported adverse reactions. In clinical trial experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents. Patients who are at risk for clinically significant leukopenia/neutropenia or clinically significant orthostatic hypotension will be excluded from the study. Orthostatic hypotension will be measured at each study visit, including follow-up.

Patients will be closely monitored during the study. Standard safety tests including orthostatic vital signs and chemistry panels (refer to Table 4) will be done at each study visit including follow-up as outlined in the Schedule of Assessments (SoA) (Appendix A); additional safety tests can be performed at the discretion of the Corcept Medical Monitor.

The effects of any excessive GR or MR antagonism should be reversible by the administration of intravenous (IV) or oral hydrocortisone and intravenous fluids (IVF). Further information for monitoring and treating excessive GR or MR antagonism is provided in Section 5.2.2 and 5.3.3.

# 2 STUDY OBJECTIVES

## 2.1 Safety Objective

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

## 2.2 Primary Efficacy Objective

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

## 2.3 Secondary Efficacy Objective

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

## 2.4 Pharmacokinetics Objective

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

# 3 STUDY DESIGN

## 3.1 Overall Design

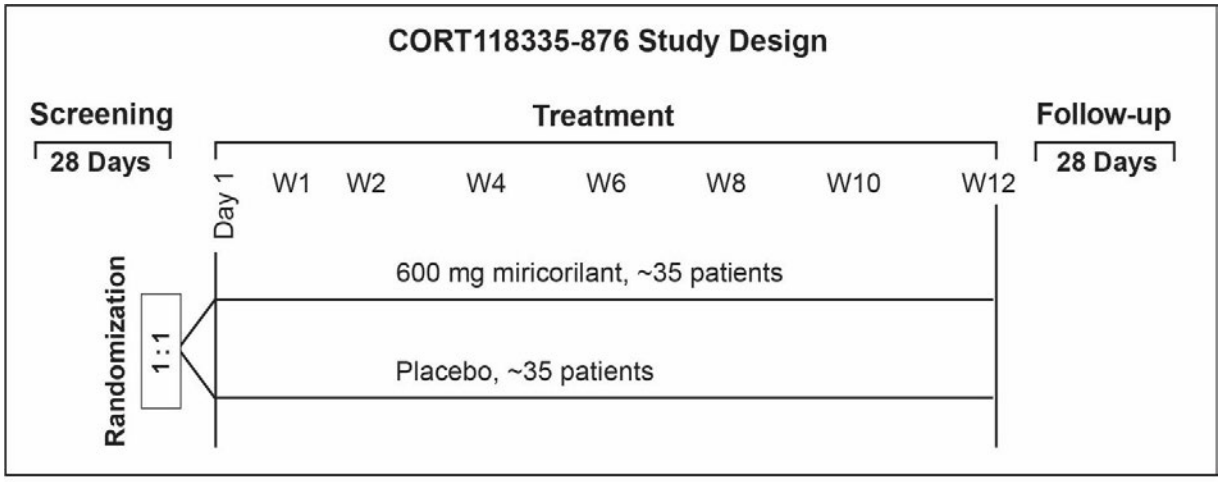
This is a randomized, double-blind, placebo-controlled multicenter study to evaluate the safety, efficacy, and PK of miricorilant in obese patients (BMI ≥30 kg/m$^2$) with schizophrenia or bipolar disorder who have recent AIWG caused by any FDA-approved oral or injectable atypical antipsychotic medication (except clozapine).

The study consists of the following study periods:

- Screening Period: up to 28 days
- Treatment Period: Day 1 to Week 12
- Follow-up Period: 28 days after last study dose

The study design is illustrated in Figure 3.

**Figure 3 CORT118335-876 Study Design**




Abbreviation: W, week.

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 approximately 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.

## 3.2 Study Endpoints

### 3.2.1 Safety Endpoints

The following endpoints will be summarized to assess the safety of miricorilant:

- Incidence of AEs, SAEs, and AEs leading to early discontinuation

- Changes from Baseline in clinical laboratory tests (hematology and chemistry panels) at Week 12
- Changes from Baseline in physical examinations and vital sign measurements at Week 12
- Changes from Baseline in ECG parameters at Week 12

### 3.2.2 Primary Efficacy Endpoint

The following endpoints will be used to evaluate the primary objective of assessing the efficacy of miricorilant compared with placebo in reversing AIWG caused by an atypical antipsychotic medication:

- Change from Baseline in body weight at Week 12 for 600 mg miricorilant versus placebo

### 3.2.3 Secondary Efficacy Endpoints

The following endpoints will be used to evaluate the secondary objective of assessing the efficacy of miricorilant in improving parameters associated with diabetes or cardiovascular morbidity

- Percentage of patients achieving a ≥5% weight loss from Baseline at Week 12 for 600 mg miricorilant versus placebo
- Change from Baseline in waist-to-hip ratio at Week 12 for 600 mg miricorilant versus placebo
- Change from Baseline in HOMA-IR at Week 12 for 600 mg miricorilant versus placebo

### 3.2.4 Exploratory Endpoints

The following exploratory endpoints will be analyzed:

In all patients:

- Change from Baseline in adrenocorticotropic hormone (ACTH) at Week 12
- 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 Structured Interview Guide for the Montgomery-Åsberg Depression Rating Scale (MADRS-SIGMA) at Week 12

In patients with diabetes:

- Change from Baseline in glycated hemoglobin (HbA1c) at Week 12
- Change in fasting blood glucose at Week 12

In patients with high blood pressure:

- Change from Baseline in blood pressure at Week 12

### 3.2.5 Pharmacokinetic Endpoint

The following endpoint will be summarized to meet the study PK objective of assessing the PK of miricorilant in patients with AIWG:

- Key PK parameters estimated from steady-state plasma concentrations

## 3.3 Number of Patients and Study Participation

### 3.3.1 Number of Patients

Approximately 70 patients will be randomized in this study, with a target of randomizing 35 patients in each treatment group: 600 mg miricorilant and placebo. See Section 9.3 for details regarding sample size calculation. See Section 4.5 for details regarding replacement of patients.

Approximately 45 patients are expected to participate in the PK substudy. Patients who consent to participate in the PK substudy but do not provide adequate samples may be replaced.

### 3.3.2 Patient Study Completion

The maximum expected duration of a patient's participation is 20 weeks (4 weeks of screening, 12 weeks of treatment, and 4 weeks of follow-up). Patients are considered to have completed the study if they complete the treatment phase of the study, including the Week 12 visit.

## 3.4 Definitions: End of Treatment, End of Study, and Study Duration

### 3.4.1 End of Treatment

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

### 3.4.2 End of Study

The end of study is defined as the date of last contact (i.e., visit, telephone, e-mail) with any study patient. Corcept will ensure that the Institutional Review Board (IRB) is notified that the study has finished according to Corcept's standard operating procedures and/or local or national regulations.

## 3.5 Study Termination by Sponsor

If Corcept, Investigator, Study Monitor, or regulatory officials discover conditions arising during the study that indicate that the study should be halted or that a study site's participation should be terminated, this action may be taken after appropriate consultation between Corcept and Investigator. Conditions that may warrant termination of the study include, but are not limited to, the following:

- Discovery of an unexpected, serious, or unacceptable risk to patients enrolled in the study
- Decision on the part of Corcept to suspend or discontinue testing, evaluation, or development of the product

Study termination and follow-up will be performed in compliance with applicable regulations.

# 4 STUDY POPULATION

The following eligibility criteria are designed to select patients with schizophrenia or bipolar disorder, and a BMI ≥30 kg/m$^2$ who have started any FDA-approved oral or injectable atypical antipsychotic medication (except clozapine) for the treatment of schizophrenia or bipolar disorder within the last 18 months prior to Screening and have since shown increase in body weight by ≥5% within 6 months of antipsychotic medication initiation either documented by medical records, treating physician's report, or by an acceptable means of patient-documented weight gain; and for whom protocol treatment is considered appropriate. All relevant medical and nonmedical conditions will be taken into consideration when deciding whether this protocol is suitable for a particular patient.

## 4.1 Inclusion Criteria

Patients eligible for enrollment into this study must meet the following criteria:

1. Have provided informed consent.
2. Are men or women ≥18 to ≤65 years old.
3. Are able to successfully complete placebo-tablet swallow assessment.
4. Meet the criteria for schizophrenia based on medical history and the Mini International Neuropsychiatric Interview (MINI) or meet the criteria for bipolar disorder as described by the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and the MINI.
5. Have started any FDA-approved oral or injectable atypical antipsychotic medication (except clozapine) for treatment of schizophrenia or bipolar disorder within 18 months of Screening. Patients with bipolar disorder will need to either be on monotherapy with an antipsychotic medication or have been on a stable dose of a mood stabilizer for ≥3 months with a stable weight and subsequently have an antipsychotic medication added that resulted in weight gain. Patients with bipolar disorder who are on a mood stabilizer must remain on a stable dose of their mood stabilizer throughout the study.
6. Have shown an increase in body weight of ≥5% above their prior body weight within 6 months of atypical antipsychotic medication initiation, as documented by medical records, physician's report, or by an acceptable means of patient-documented weight gain.
    a. Historical weights from medical records must be within 6 months prior to initiation of antipsychotic medication.
        i. Patients who have had a treatment gap in their antipsychotic medication for ≥28 days but have restarted medication within 18 months of Screening are eligible to participate if they have documented increase in body weight of ≥5% within 6 months of restarting the antipsychotic medication. Historical weights will not be accepted for these patients.
        ii. Historical weights will not be accepted for patients with bipolar disorder on mood stabilizers.
    b. Patients who document their own weight gain MUST show evidence of weight gain using one of the following methods: 1) using Smart Scale weight data, 2) using photographs to record weight displayed on a scale, or 3) using a weight diary.

i. Dates of weight collection need to be available for the weight gain documentation method used.
   - The scale photograph must clearly show the scale and displayed weight. The photograph must show the date and time stamp for inspection and verification by the study staff.

ii. Historical "prior body weight" before the initiation of their antipsychotic medication will not be accepted for patient-documented weight.

7. Have been on the same dose of oral or injectable atypical antipsychotic medication for the last month prior to Screening.
8. Are clinically stable and unlikely to require changes to their antipsychotic medication (i.e. medication switch or dose change) through the duration of the study (20 weeks).
9. Have a BMI ≥30 kg/m$^2$.
10. Patients with schizophrenia must have a BPRS of ≤50 at Screening.
11. Patients with bipolar disorder must have a YMRS of ≤20 and MADRS-SIGMA of ≤20 at Screening.
12. Agree to use a highly effective method of contraception throughout the study and for at least 28 days after the last dose of assigned treatment (if a woman of childbearing potential or a man with a sexual partner of childbearing potential; see Section 4.6). Men with partners of childbearing potential must agree to use 2 forms of contraception, one of which is a double barrier method. Men must also agree to avoid sperm donation during the study and for at least 28 days after the final treatment administration.

## 4.2 Exclusion Criteria

Patients who meet any of the following criteria will not be eligible to participate in the study:

1. Have psychiatric exclusion criteria:
   a. An acute psychiatric condition that might require emergent intervention during the study.
   b. A psychiatric hospitalization within the last 6 months prior to Screening.
   c. Are currently at risk of suicide in the opinion of the Investigator or as confirmed by the following:
      i. Answer "Yes" on items 4 or 5 (C-SSRS-ideation) with the most recent episode occurring within the last 6 months prior to Screening.
      ii. Answer "Yes" to any of the 5 items (C-SSRS-behavior) with an episode occurring within the last 6 months prior to Screening.
2. Have participated in another Corcept study with miricorilant.
3. Are currently taking the antipsychotic medication clozapine.
4. Are currently taking the mood stabilizing medication carbamazepine.
5. Are currently taking more than one antipsychotic medication.
6. Have poorly controlled diabetes mellitus with HbA1c >10% or a fasting blood glucose >200 mg/dL.
7. Have poorly controlled hypertension with a systolic blood pressure >170 mm Hg or a diastolic blood pressure >100 mm Hg by in-office blood pressure measurement.
8. Have a history of symptomatic hypotension with a systolic blood pressure <100 mm Hg or a diastolic blood pressure <60 mm Hg.

9. Have a recent history of orthostatic hypotension with a systolic blood pressure decrease of at least 20 mm Hg or a diastolic blood pressure decrease of at least 10 mm Hg within the last year prior to Screening.
10. Have a history of a seizure disorder.
11. Are currently using or plan to use prescription or over-the-counter weight-loss treatments, including but not limited to*:
    a. Olanzapine/samidorphan (Lybalvi) or other samidorphan drug combinations.
    b. Prescription drugs such as orlistat (Xenical), phentermine (Adipex-P, Pro-Fast SA, Pro-Fast SR, Fastin, Oby-trim, Zantryl, Teramine, Phentride, Phentercot, Obephen, Oby-cap), phentermine/topiramate (Qsymia), liraglutide (Saxenda), semaglutide (Wegovy), or naltrexone HCl/bupropion HCl (Contrave).
    c. Over-the-counter anti-obesity agents such as orlistat (Alli), herbal supplements or other alternative remedies (Cortislim, Dexatrim, Acutrim).

    *Patients currently taking these medications may participate in the study if appropriate to discontinue the medication, and if the patient is amenable to discontinuing the medication for a wash-out period of 5 half-lives prior to the baseline assessment.

    Note: Names within parenthesis are trademarks of third-party companies.
12. Are currently using any prohibited medications (Section 5.4.3). Prohibited medications must be discontinued at least 5 half-lives prior to a patient receiving their first study treatment. Administration of concomitant medications (Section 5.4) are at the discretion of the Investigator and/or Medical Monitor.
13. Have a history of a medical condition affecting body weight including but not limited to poorly controlled hyper- or hypothyroidism; eating disorder such as anorexia, bulimia, or binge eating; or polycystic ovary syndrome.
14. Have had weight-loss surgery including, but not limited to, gastric bypass, sleeve gastrectomy, gastric band placement, or biliopancreatic diversion with duodenal switch within the last 5 years prior to Screening or are planning weight-loss surgery during the study.
15. Have had liposuction within 1 year prior to Screening or have planned liposuction during the study.
16. Have any elective surgery planned during the study.
17. Have the following laboratory abnormalities:
    a. Serum sodium ≤130 mmol/L or ≥145 mmol/L.
    b. Serum potassium ≤3.5 mEq/L or ≥5.1 mEq/L.
    c. Estimated glomerular filtration rate <60 mL/min/1.73m$^2$.
    d. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 × the upper limit of normal.
    e. White blood cell count (WBC) below the limit of normal.
    f. Absolute neutrophil count <1,500 neutrophils/µL.
18. Have a clinically significant electrolyte abnormality at Screening.
19. Are currently using a medication such as digoxin with an increased risk for toxicity in the event of electrolyte changes.
20. Are taking an unstable dosage (change in the dose within 4 weeks prior to Screening) of a medication that may change the fluid or electrolyte status such as a diuretic.

21. Have a clinically significant ECG abnormality as judged by the Investigator.
22. Have a QTcF >450 ms for men or QTcF >470 ms for women.
23. Are breast feeding, or pregnant, or planning a pregnancy.
24. Have any clinical condition or significant concurrent disease judged by the Investigator to complicate the evaluation of the study treatment.
25. Previous exposure to investigational drugs taken within 3 months or 5 half-lives of the investigational drug prior to Screening, whichever is longer.
26. Are employees or immediate family members of the clinical site staff or Corcept employees.
27. Have a current or prior history within the last 12 months of severe alcohol-use disorder, severe tobacco-use disorder, or severe cannabis use disorder as defined by the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).
28. Have a history of illicit drug use within the last 12 months including but not limited to cocaine, heroin, ecstasy, lysergic acid diethylymide (LSD) or other hallucinogens, and ketamine.
29. Are seropositive for, hepatitis B or hepatitis C.
30. Patients with a known HIV infection.
31. Have an allergic reaction or hypersensitivity to miricorilant tablets.

## 4.3 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently randomly assigned to study treatment.

Patients who have an exclusionary laboratory, ECG, or vital sign result on initial screening tests may have that assessment repeated once within the 28-day screening period if the Investigator believes the result was spurious or otherwise confounded.

Individuals who do not meet the criteria for participation in this study (screen failure) because of laboratory abnormalities alone may be rescreened at the discretion of the Investigator in discussion with the Medical Monitor. Rescreened patients should be assigned a new patient number. Rescreened patients should meet all of the entry criteria outlined in Sections 4.1 and 4.2.

## 4.4 Early Patient Discontinuation or Withdrawal

In this study, patient “discontinuation” refers to early discontinuation of study treatment while remaining on study; that is, the patient may wish to stop treatment early but may agree to continue with study visits and/or assessments.

Early patient “withdrawal” refers either to patient withdrawal of consent to any further study participation or to an Investigator/Sponsor decision to permanently withdraw the patient and cessation of all study treatments, procedures, and assessments without further follow-up. If a patient wishes to withdraw consent to further participation in the study entirely, this should be clearly documented (1) in the patient’s medical record and signed by the Investigator and (2) in the clinical study database (electronic case report form [eCRF]).

### 4.4.1 Early Patient Discontinuation

Study treatment may be discontinued in the event of any of the following occurrences:

- Unacceptable toxicity.
- The Investigator decides it is in the patient's best interest to discontinue treatment and/or participation in the study. Reasons may include the following:
  - The patient requires prohibited medications.
  - The patient is not compliant with protocol requirements.
- Patient becomes pregnant.

If a patient discontinues early from the study drug, that patient will complete an Early Termination (ET) visit at the time of the last dose of the study drug, or soon thereafter. The Follow-Up visit will be conducted 28±5 days after the last dose of the study drug. Investigators should encourage these patients to continue with all study visits and/or assessments per the patient's original study schedule through Week 12 (end-of-treatment). If the Follow-Up visit coincides with any other study visit, the assessments performed at these visits will be combined. If a patient is unable to continue with all study visits, they will be encouraged to complete the end-of treatment Week 12 visit at the very least, in addition to the ET and Follow-Up visits. The date when the patient discontinues treatment and the reason for discontinuation must be recorded on the eCRF.

For guidelines about temporary interruption of treatment, see Section 5.3.

### 4.4.2 Early Patient Withdrawal from Study

A patient may be withdrawn early from the study for the following medical or administrative reasons:

- Withdrawal of consent.
- Noncompliance, including refusal of the study treatment and/or failure to adhere to the study requirements, as specified in protocol.
- Early termination of the study by Corcept.

The date the patient is withdrawn from the study and the primary reason for withdrawal must be recorded on the eCRF.

Patients may withdraw voluntarily from the study at any time. For patients who withdraw consent to participate in the study, every effort should be made to determine whether the withdrawal of consent was related to an AE or a specific aspect of the study.

## 4.5 Replacement of Patients

Patients who withdraw from study early may be replaced, at the discretion of Corcept and the Investigator, to ensure that sufficient patients complete the study to achieve the objectives. A patient who is withdrawn because of AEs considered related to study medication will not be replaced.

## 4.6 Restrictions During Study

The following restrictions apply to patients in this study (prohibited or limited-use medications are described in Section 5.4):

**Dietary Restrictions**: Patients will be asked to follow a healthy diet according to the American Heart Association guidelines (AHA 2018).

**Alcohol**: Patients will be advised to limit alcohol use (also see Section 4.2 regarding alcohol consumption).

**Pregnancy**: Miricorilant should not be administered to pregnant women due to adverse effects on fetal development (mice) or adverse pregnancy outcomes (rabbits). Therefore, women of childbearing potential must not become pregnant during this study. Men and women of childbearing potential who participate in this study must agree to use effective contraception.

a. Highly effective forms of contraception include:
   i. Abstinence
   [Abstinence is only acceptable as true abstinence (i.e., when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a study, and withdrawal are not acceptable methods of contraception.]
   ii. Intrauterine device or intrauterine system
   iii. Oral contraceptive plus a barrier method
   iv. Diaphragm with vaginal spermicidal cream
   v. Vaginal spermicide with a condom
   vi. Surgical sterilization (≥6 months postsurgery)

b. A patient is of childbearing potential if, in the opinion of the Investigator, she is biologically capable of having children and is heterosexually active.
   i. Women who are not of childbearing potential meet at least 1 of the following criteria:
      - Have undergone a documented hysterectomy and/or bilateral oophorectomy.
      - Have medically confirmed ovarian failure or have reached postmenopausal status, defined as cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and have a serum follicle stimulating hormone (FSH) level within the laboratory's reference range for ovarian failure or postmenopausal women.

**Activity**: Patients will be advised to continue their normal activity level and avoid excessive exertion beyond their normal activities.

# 5 STUDY TREATMENTS AND MANAGEMENT

## 5.1 Study Drug and Placebo

Study drug and placebo equivalent, including dose and regimen, formulation, packaging, and storage, are described in Table 1. A placebo tablet dosage form is developed to match the miricorilant 100-mg tablets.

**Table 1 Study Drug and Placebo: Formulation, Administration, Packaging, and Storage**

| Specifications | Miricorilant | Placebo |
|---|---|---|
| Description | Miricorilant tablets are white to off-white in color. | Placebo tablets are white to off-white in color. |
| Unit Dose Strength | Miricorilant 100-mg tablets. | Matching placebo tablets. |
| Dose levels | 600 mg | Placebo equivalent. |
| Administration | Orally, with 8 oz (240 mL) of water. Take with food. | Orally, with 8 oz (240 mL) of water. Take with food. |
| Regimen | 6 tablets, once daily at approximately the same time each day [a]. Swallow tablets whole. Do not chew, crush, cut, or dissolve the tablets. | 6 tablets, once daily at approximately the same time each day [a]. Swallow tablets whole. Do not chew, crush, cut, or dissolve the tablets. |
| Dispensing study drug | Dispense to patients according to their visit schedule. | Dispense to patients according to their visit schedule. |
| Missed doses | If the patient remembers they missed a dose within 12 hours of their normally scheduled dosing time, then they should take their daily dose of study drug and then resume normal schedule. | If the patient remembers they missed a dose within 12 hours of their normally scheduled dosing time, then they should take their daily dose of study drug and then resume normal schedule. |
| Supplied | Tablets, 42-count in child-resistant blister packaged cards and labeled per country requirement. | Tablets, 42-count in child-resistant blister packaged cards and labeled per country requirement. |
| Storage | Store as follows:<br>• In a secure location.<br>• At 20°C–25°C (68°F–77°F), excursions permitted to 15°C–30°C (59°F–86°F).<br>• Out of sight and reach of children. | Store as follows:<br>• In a secure location.<br>• At 20°C–25°C (68°F–77°F), excursions permitted to 15°C–30°C (59°F–86°F).<br>• Out of sight and reach of children. |

Procedures for inventory, reconciliation, and destruction or return of study tablets are provided in Section 11.5.
a. Participants who participate in the PK substudy must take their medication in the morning.

## 5.2 Safety Assessments

### 5.2.1 Monitoring of Liver Injury

Any patient experiencing signs and symptoms consistent with liver injury, such as a combination of nausea, vomiting, anorexia, fatigue, and/or right upper quadrant abdominal pain or discomfort, should undergo immediate testing prior to their next scheduled visit for ALT, AST, GGT, total and direct bilirubin, alkaline phosphatase, prothrombin time (PT), and international normalized ratio (INR). Should the patient have laboratory evaluations consistent with suspected liver injury, actions as outlined in Table 2 should be taken.

### 5.2.2 Excessive GR/MR Antagonism

Based on the mechanism of action of miricorilant, there is a theoretical risk of excessive GR antagonism and excessive MR antagonism. Excessive GR antagonism could manifest with findings such as weakness, tiredness, dizziness, orthostatic hypotension, hypoglycemia, dehydration, nausea, vomiting, diarrhea, and muscle aches. Excessive MR antagonism could manifest as hyperkalemia, dehydration, and hypotension; hypotension may be seen in the absence of antihypertensive medication. These symptoms should be monitored throughout the duration of the clinical trial both during treatment period (including Baseline) and in the follow-up period. If excessive GR and MR antagonism is suspected, patients should discontinue the study medication, and administration of intravenous fluids (IVF), and intravenous (IV) or oral hydrocortisone begun without delay and the actions outlined in Table 2 should be taken. The half-life of miricorilant is approximately 21 to 23 hours. Symptoms should continue to be monitored even after the last dose of study medication in the follow-up period.

## 5.3 Dose Adjustment Criteria

### 5.3.1 Dose Reduction

No dose modification will be allowed.

### 5.3.2 Dose Interruption and/or Discontinuation: General Criteria

All attempts should be made to continue patients on the study for the duration of the study. However, study treatment can be temporarily interrupted up to 5 days if deemed necessary by the Investigator. Upon interrupting the study treatment, the Investigator should consult the Corcept Medical Monitor. Before restarting study treatment, the Investigator must obtain approval from the Corcept Medical Monitor. If the event that necessitated treatment interruption recurs after study treatment is restarted, the patient should be permanently discontinued from study treatment. In addition, patients will be permanently discontinued from study treatment if they experience any of the criteria listed for stopping treatment in Table 2.

### 5.3.3 Dose Interruption and/or Discontinuation: Special Safety Events

Guidelines for temporarily interrupting and restarting and for permanently discontinuing study treatment due to safety events (excessive GR or MR antagonism; hyperkalemia; hypotension; suspected liver injury; or significant trauma, surgery, or medical illness) are outlined in Table 2.

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

| Safety Event | Criteria for Interrupting and Restarting Study Treatment and Patient Management | Criteria for Stopping Study Treatment |
|---|---|---|
| Excessive GR or MR antagonism | Criteria: signs and symptoms of excessive GR and MR antagonism (Section 1.5)<br>Management:<br>• ***Immediately interrupt miricorilant treatment*** for ≥5 days and start standard supportive care, including IV fluids, as indicated.<br>• If appropriate, administer supplemental glucocorticoids given in high doses to overcome the GR antagonism produced by miricorilant. Initially, consider parenteral hydrocortisone, followed by additional IV or oral doses once or twice daily for 1 to 3 days and tapered thereafter, depending on clinical response. In some cases, higher doses of hydrocortisone for longer periods of time may be required.<br>• If the patient has been receiving treatment with a MR antagonist, consider discontinuing it, particularly in the presence of hypotension.<br>• Restart miricorilant treatment only if the workup reveals an alternative cause for symptoms of possible excessive GR/MR antagonism and after consultation with the Corcept Medical Monitor. | A combination of the following Grade 3 or higher events:<br>fatigue, anorexia, nausea, and vomiting (associated with decreased oral intake), and abdominal pain. |
| Hypotension | Criteria: development of hypotension while on study treatment.<br>Management:<br>• Confirm the diagnosis by in-office BP monitoring and orthostatic BP measurements.<br>• Examine patient and check potassium levels.<br>• If appropriate, advise the patient to hydrate orally with electrolyte containing hydration (e.g., Gatorade or Pedialyte). Hypotension can also be support with IV hydration with isotonic fluids.<br>• Patients who have hypotension should have any antihypertensive medications and diuretic medications discontinued as appropriate.<br>• Interrupt miricorilant if SBP <100 mm Hg or if DBP <60 mm Hg or if orthostatic hypotension is present or if patient requires treatment with IV fluids. | SBP <100 mm Hg or DBP <60 mm Hg (as confirmed by in-office BP measurements) or orthostasis, despite the discontinuation of antihypertensive medications and IV and oral hydration. |

| Safety Event | Criteria for Interrupting and Restarting Study Treatment and Patient Management | Criteria for Stopping Study Treatment |
|---|---|---|
| | • Restart miricorilant only if hypotension is transient and reversible and not related to study medication, and after consultation with the Corcept Medical Monitor. | |
| Hyperkalemia | Criteria: development of hyperkalemia during the study,<br>Management:<br>• Verify hyperkalemia and normal renal function.<br>• Obtain ECG for evaluation of hyperkalemia.<br>• Interrupt miricorilant if hyperkalemia is severe (>6.0 mEq/L) or if renal function is impaired.<br>• As medically indicated, initiate treatment for hyperkalemia.<br>• Restart miricorilant only if the underlying cause of hyperkalemia is transient and correctable and after discussion with the Corcept Medical Monitor. | Severe (>6.0 mEq/L) hyperkalemia<br>Confirmed ECG abnormalities including peaked T waves, shortened QT interval, ST segment depression, prolonged PR interval, flattened p wave, widened QRS, amplified R wave, or intraventricular/ fascicular/bundle branch blocks.<br>Underlying renal disease. |
| Suspected liver injury | Criteria: AST or ALT >3 × ULN or total bilirubin >2.0 × ULN while on study drug<br>Management:<br>• Repeat liver biochemistries (ALT, AST, alkaline phosphatase, total bilirubin) within 48 to 72 hours of results.<br>• Obtain a more detailed history of symptoms and prior or concurrent disease and a history of concomitant drug use (including nonprescription medication and herbal and dietary supplement preparations).<br>• Obtain a history of exposure to environment chemical agents.<br>• Rule out other causes of liver disease.<br>• Obtain additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).<br>• Continue to monitor the liver biochemistry two or three times weekly but no less frequently than once weekly. Frequency can decrease to once a week or less if abnormalities stabilize, or study drug has been discontinued and the patient is asymptomatic.<br>• Consider a gastroenterology or hepatology consultation. | Study drug will be stopped if:<br>• ALT or AST >5 × ULN.<br>• ALT or AST >3 × ULN and (TBL >2 × ULN or INR >1.5).<br>• ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%). |

| Safety Event | Criteria for Interrupting and Restarting Study Treatment and Patient Management | Criteria for Stopping Study Treatment |
|---|---|---|
| | • During the period of close observation, study drug can be continued if desired at the discretion of Corcept Medical Monitor and Investigator unless one of the criteria for stopping study treatment are met. | |
| Significant trauma, surgery, or medical illness at any time during the study (through 2 weeks after last dose) | Management:<br>• As medically indicated, interrupt miricorilant treatment and provide supplemental hydrocortisone to offset the GR antagonism even in patients not experiencing signs and symptoms of excessive antagonism.<br>• After resolution of the physiological stress associated with the event and if still within the Treatment Period, resume miricorilant. | Patient does not recover from the significant trauma, surgery, or medical illness within the Treatment Period. |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; DBP, diastolic blood pressure; ECG, electrocardiogram; GR, glucocorticoid receptor; INR, international normalized ratio; IV, intravenous; MR, mineralocorticoid receptor; SBP, systolic blood pressure; TBL, total bilirubin level; ULN, upper limit of normal.

## 5.4 Concomitant Medications

Miricorilant is primarily eliminated hepatically by CYP2C19 and exhibits inhibitory potential of CYP3A4, CYP2C8, CYP2C9, UGT1A1, and BCRP in vitro (Section 1.2.2). Concomitant medications that have overlapping enzyme/transporter pathways with miricorilant must be evaluated for potentially clinically relevant drug-drug interactions. Accordingly, the coadministration of concomitant medications in this study is at the discretion of the Principal Investigator and/or Corcept Medical Monitor.

### 5.4.1 Permitted Concomitant Medications

Medications required to treat AEs, manage symptoms, concurrent diseases, and supportive care agents, such as pain medications, anti-emetics, and antidiarrheal agents, are allowed at the discretion of the Principal Investigator and/or Corcept Medical Monitor. Patients must be instructed to notify the investigational site about any new medications they take after the start of study treatment. All medications (other than study treatments) administered 30 days before study entry (i.e., after a patient signs the ICF) and during the study must be listed on the concomitant medications eCRF.

Permitted concomitant medications are listed in Table 3.

**Table 3 Permitted Concomitant Medications**

| Medication | Use and/or Restriction |
|---|---|
| Antipsychotic medication | No change to the antipsychotic medication during the study duration through the Follow-Up Visit |
| Insulin and oral antidiabetic medication | Dose may be decreased or stopped during study treatment to prevent hypoglycemia. Do not add new antidiabetic medication or titrate existing medication up without prior consultation with the Corcept Medical Monitor. |
| Antihypertensive medication | Dose may be decreased or stopped during study treatment to prevent hypotension or orthostatic symptoms. Do not increase dose or add new antihypertensive medications without prior consultation with the Corcept Medical Monitor. |
| Lipid-lowering drug | No increases in current dose allowed from 4 weeks before Baseline through the Follow-up Visit. |
| Antidepressant medication | No restrictions unless there is a potential DDI. |
| Anxiolytic medication such as benzodiazepines | No restrictions unless there is a potential DDI. |

### 5.4.2 Permitted Concomitant Therapy Requiring Caution

Permitted concomitant medications to be used with caution from 1 week before Baseline through the Follow-up Visit are as follows:

- Moderate inhibitors or inducers of CYP2C19.

- Substrates metabolized predominantly by CYP3A4, CYP2C8, and/or CYP2C9 with a narrow therapeutic index.
- Strong inhibitors of CYP3A4, CYP2C8, and/or CYP2C9.
- Medications that carry a possible risk for QT prolongation.

### 5.4.3 Prohibited Medications

The following medications are prohibited during treatment with miricorilant in this study:

- Antipsychotic medication clozapine.
- Mood stabilizing medication carbamazepine.
- Other investigational therapies.
- Digoxin or other medications with increased risk for toxicity in the event of electrolyte changes.
- Prescription or over-the-counter medications that are strong inducers or strong inhibitors of CYP2C19 are prohibited.
- Systemic corticosteroids, including inhaled corticosteroids (with exception of temporary use for treatment of excessive GR antagonism), potent (group III) topical corticosteroids, and intra-articular corticosteroids
- Prescription or over-the-counter weight-loss treatments, including but not limited to:
  - Olanzapine/samidorphan (Lybalvi) or other samidorphan drug combinations.
  - Prescription drugs such as orlistat (Xenical), phentermine (Adipex-P, Pro-Fast SA, Pro-Fast SR, Fastin, Oby trim, Zantryl, Teramine, Phentride, Phentercot, Obephen, Oby-cap), phentermine/topiramate (Qsymia), liraglutide (Saxenda), semaglutide (Wegovy), or naltrexone HCl/bupropion HCl (Contrave).
  - Over-the-counter anti-obesity agents such as orlistat (Alli), herbal supplements, or other alternative remedies such as Cortislim, Dexatrim, Acutrim.

## 5.5 Method of Treatment Assignment and Randomization

All patients will be centrally randomized to study treatment using an interactive web response system (IWRS). Permuted block randomization will be used to ensure approximate balance among treatment groups. Before the study is initiated, the log-in information and directions for the IWRS will be provided to each site.

Study treatment will be dispensed at the study visits summarized in the Schedule of Assessments (SoA) (Appendix A).

Returned study treatment should not be re-dispensed to patients. However, study treatment brought back by the patient for accounting reasons can be returned to the patient.

## 5.6 Blinding

This is a double-blind, placebo-controlled study. Tablets containing 100 mg miricorilant or placebo will be identical in appearance.

The Sponsor or designee, the Investigator, the Corcept Medical Monitor, study-site personnel, and the patient will be blinded to the study drug and will not be allowed to view the results of

laboratory tests that have the potential to reveal a patient's treatment arm due to the expected effect of the active treatment on the analyte involved.

The IWRS will be programmed with blind-breaking instructions. The blind may be broken if, in the opinion of the Investigator, it is in the patient's best interest for the Investigator to know the study treatment assignment. To maintain the overall quality and legitimacy of the clinical trial, unblinding should occur in exceptional circumstances. These circumstances could include but are not limited to pregnancy of the patient or pregnancy of the patient's partner. Corcept must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the patient's condition (e.g., antidote available). In this case, Corcept must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable.

## 5.7 Dose Diary

A dose diary will be provided, and patients will be instructed to bring their dose diary to each clinic visit. Patients should complete an entry in the diary for each self-administered dose of miricorilant. Entries will include the number of tablets and the date and time of miricorilant administration. Time and dose administered should be documented in the clinic charts.

## 5.8 Product Accountability and Treatment Adherence

Patients will be instructed to return all unused study tablets when they come in for each clinic visit. Study treatment adherence will be determined by review of the dose diary (Section 5.7) and counting returned tablets. On visit days, study treatment should be taken in the clinic during the visit and after initial blood draws.

A patient who is assigned a study treatment (i.e., 600 mg miricorilant or placebo) will be considered nonadherent if he or she misses >30% of the prescribed doses during the study, unless the patient's study treatment was withheld by the Investigator for safety reasons. Similarly, a patient will be considered nonadherent if he or she is judged by the Investigator to have intentionally or repeatedly taken more than the prescribed amount of study treatment. Patients found to be nonadherent with their assigned treatment regimen should be assessed to determine the reason for nonadherence and educated and/or managed as deemed appropriate by the Investigator to improve adherence.

## 5.9 Independent Data Monitoring Committee to Monitor Patient Safety

An Independent Data Monitoring Committee (IDMC) will be established to conduct periodic reviews of data to ensure the safety of patients. The IDMC will be composed of at least 4 voting members: three physicians and one statistician, who, collectively, have endocrinology, psychiatry, and hepatology experience in the treatment of patients with schizophrenia or bipolar disorder and in the conduct and monitoring of randomized clinical trials. The IDMC will meet at least quarterly. Further details describing the IDMC composition, contents of data reports, responsibilities, and decision rules will be described in the IDMC Charter.

# 6 DESCRIPTION OF STUDY ASSESSMENTS AND PROCEDURES AND APPROPRIATENESS OF MEASUREMENTS

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

The Investigator and Sponsor will conduct the study in accordance with International Council on Harmonisation (ICH) Good Clinical Practice (GCP) and local regulations. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct, and the Investigator must ensure that trial procedures are performed as described in the protocol. During the study, procedures and observations will be monitored to confirm that study requirements are being followed as outlined in the SoA.

In the event that a patient is unable to come to the clinic to participate in study-related visits or procedures, sponsor-approved alternative options may be provided to the Investigator sites based on the needs and safety of patients. This may include the provision of study-drug dispensation and delivery outside of a clinic visit.

## 6.1 Informed Consent and Screening

Written informed consent must be obtained before initiating any study-mandated procedures.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the patient's routine clinical management (e.g., blood count) and obtained before signing of the informed consent form (ICF) may be used for Screening or Baseline purposes, provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Appendix A).

## 6.2 Placebo Tablet Swallow Assessment

Patients will be asked to swallow 6 placebo tablets during screening to ensure ability to participate in the study. These placebo tablets will be administered with 8 oz (240 mL) of water and may be taken with or without food.

## 6.3 History

Medical history, including details regarding surgeries, illnesses and allergies, date(s) of onset, and whether conditions are currently ongoing, and medication history will be collected on all patients during Screening. Medical history will be updated at the Day 1 Visit and will then serve as the baseline for other clinical assessments.

## 6.4 Safety Measures

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

### 6.4.1 Physical Examination and Vital Signs

Physical examinations including a basic neurologic examination will be performed at every visit during the study and at Follow-Up.

Vital signs will be measured at every visit during the study and include resting heart rate, blood pressure, respiratory rate, and body temperature. Systolic and diastolic blood pressure, measured in mm Hg, will be measured after patients have been at rest (seated) for ≥3 minutes. Heart rate, measured in beats per minute, will be taken after the patient has been in a resting state (seated) for ≥3 minutes. The heart rate should be recorded over 30 seconds or longer.

Orthostatic vital signs should be performed for all patients at every visit. Heart rate and blood pressure should be taken first in a supine state at rest (lying for ≥3 minutes). Patient should then be instructed to stand and heart rate and blood pressure should be repeated 3 minutes after the patient has stood.

Unscheduled assessments of vital signs can be performed as necessary.

### 6.4.2 Height

Height will be measured once, at Screening.

### 6.4.3 Electrocardiogram

Twelve-lead ECG tracings will be obtained in triplicate from all patients at every visit during the study. Patients should be lying down resting for approximately 15 minutes before each ECG evaluation. It is acceptable to start taking ECG 1-minute prior. A central reviewer will be used; instruction will be provided in the imaging manual.

The Investigator or designee will indicate on the site's copy whether the ECG was normal, abnormal but not clinically significant, or abnormal and clinically significant. Any new or worsened abnormality noted as clinically significant will be reported as an AE.

### 6.4.4 Adverse Events

Details on definitions and reporting of AEs are provided in Section 8.

All AEs will be recorded from the time of signing the ICF until 28 days after the last dose of study treatment. Patients should be monitored for AEs and AEs assessed for expectedness consistent with the current IB for miricorilant. To help characterize any possible relationships between drug exposure and the clinical event, when an SAE occurs, ACTH and cortisol should be assessed as close to the time of the event as possible, and a PK sample may be drawn at the discretion of the Investigator.

### 6.4.5 Clinical Laboratory Assessments

#### 6.4.5.1 Laboratory Parameters

Blood samples will be collected for the analysis of safety in all patients at the times indicated in the SoA (Appendix A). Laboratory samples will be analyzed at central or local laboratories as appropriate.

Laboratory values for an analyte that are outside of the normal range per the central or local laboratory will be identified and should be assessed as clinically significant or not and repeated at the Investigator's discretion. The CTCAE grading for severity of abnormal labs should be applied for consistency in the evaluation and grading assessment.

The Investigator will review all laboratory reports, evaluate the results, and sign/date the report.

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

**Table 4 Clinical Laboratory Variables Evaluated During the Study**

| **Hematology** | **Serum Chemistry** | **Urinalysis** |
|---|---|---|
| Red blood cell count<br>Hemoglobin<br>Hematocrit<br>Mean corpuscular hemoglobin<br>Mean corpuscular hemoglobin volume<br>Mean corpuscular volume<br>Platelet count<br>Mean platelet volume<br>Red blood cell distribution width<br>White blood cell count<br><br>White blood cell count with 5-part differential<br>Neutrophils (percent and absolute)<br>Lymphocytes (percent and absolute)<br>Monocytes (percent and absolute)<br>Eosinophils (percent and absolute)<br>Basophils (percent and absolute) | Sodium<br>Potassium<br>Calcium<br>Chloride<br>Phosphorus<br>Magnesium<br>Creatinine<br>Bilirubin (total and direct)<br>Albumin<br>Alkaline phosphatase<br>Lactate dehydrogenase<br>Aspartate aminotransferase<br>Alanine aminotransferase<br>Glucose (fasting)<br>Blood urea nitrogen<br>Uric acid<br>Bicarbonate<br>Total protein<br>Gamma-glutamyl transferase | Drug screen<br>**Pharmacokinetics**<br>Miricorilant and its metabolites<br>**Pregnancy**<br>Serum/urine pregnancy test (for women of childbearing potential)<br>**Thyroid Function**<br>Thyroid-stimulating hormone<br>Free thyroxine (T4) |
| **Lipid Panel** | **Hormones** | **Ad Hoc Testing** |
| Total cholesterol<br>Direct Low-density lipoprotein-cholesterol-c<br>High-density lipoprotein-cholesterol<br>Very low-density lipoprotein cholesterol<br>Triglycerides (fasting only) | Follicle-stimulating hormone<br>Hypothalamic-pituitary-adrenal (HPA)-axis parameters:<br>Plasma adrenocorticotropic hormone (ACTH) (morning)<br>Serum cortisol (morning) | Prothrombin time (PT)/international normalized ratio (INR)<br>Activated partial thromboplastin time (aPTT)<br>Creatine kinase<br>Virus screen (hepatitis A, B, and C viruses)<br>Antinuclear antibodies (ANA)<br>Anti-smooth muscle antibodies (ASMA)<br>Anti-liver-kidney microsome (anti-LKM) |
| **Glycemic Parameters** | | |
| Glycated hemoglobin (HbA1c)<br>Serum insulin (fasting)<br>Plasma glucose (fasting) | | |

Note: See Appendix A for the laboratory test schedule; ad hoc testing will be performed at the discretion of the Corcept Medical Monitor (hepatitis B and hepatitis C testing will be performed at Screening as listed in Appendix A and may also be performed on an ad hoc basis as needed).

#### 6.4.5.2 Sample Collection, Preparation, and Shipping

Instructions for collection, preparation, and shipping of all laboratory samples will be provided in the study laboratory manual. Long-term retention of biological samples is described in Section 11.4.

#### 6.4.5.3 Blood Volume Summary

Blood samples will be taken for analysis of safety laboratory, efficacy, and PK parameters, at the time points indicated in the SoA (Appendix A). The total volume of blood to be collected from each patient will be specified in the ICF.

### 6.5 Efficacy Assessments

The key primary efficacy assessment in this study is body weight measurement. The secondary efficacy measurement is waist-to-hip ratio.

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

Waist circumference will be measured for all patients at every visit. Clinical sites will be provided with tape measures to ensure consistency of circumference measurements. Waist circumference should be measured midway between the lower rib margin and iliac crest. Hip circumference should be measured at the level of the widest circumference over the greater trochanters. Detailed instructions for measurements of the waist and hip circumferences will be provided in the study manual.

The waist-to-hip ratio will be calculated as the ratio of the circumference of the waist to the hip.

### 6.6 Pharmacokinetic Assessments

Blood samples will be collected for measurement of plasma concentrations of miricorilant and its relevant metabolites as specified in the SoA (Appendix A). Instructions for the collection and handling of biological samples will be provided in the study manual. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples collected for analyses of miricorilant plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study. Refer to Section 9.4.6 for a description of variables to be analyzed.

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

### 6.7 Pharmacodynamic/Biomarker Assessments

The development and improvement of therapies increasingly depends on insights gained from analysis of biomolecules. During this study and with the consent of patients (see Section 10.3.1), biological samples (e.g., blood, plasma, serum, or tumor tissue) will be obtained, some for analysis during the study and others for future analysis of genes or proteins at the time points specified in Appendix A. These samples will be used to develop a better understanding of the mechanisms of both treatment response (predictive biomarkers) and disease processes

(prognostic biomarkers) and ultimately to identify which patients have a high probability to benefit from treatment with miricorilant and which do not.

## 6.8 Clinician Assessed Outcomes

The clinician assessed outcome assessments in the study include the BPRS, C-SSRS, and CGI. A brief description of each is provided below.

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 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.

The CGI is a scale used to assess the patient's global functioning. The CGI has 2 components—the CGI-Severity (CGI-S), which rates illness severity, and the CGI-Improvement (CGI-I), which rates change from the initiation (baseline) 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 CGI-I also asks the Investigator 1 question: "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. Both ratings are based on observed and reported symptoms.

The MADRS-SIGMA 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, and 10) Suicidal thoughts. Each question yields a score from 0–6; higher MADRS-SIGMA score indicates more severe depression.

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.

## 6.9 Appropriateness of the Measures

All efficacy and safety measurements are well-validated and the standard measurements in this patient population are appropriate for this study.

# 7 STUDY ASSESSMENTS AND PROCEDURES BY STUDY VISIT

The schedule of assessments is provided in Appendix A.

Corcept will be promptly notified of any protocol deviations.

The acceptable visit window for all visits during the Treatment Period is ±2 days and the acceptable visit window for the Follow-up Period is ±5 days.

## 7.1 Screening Period (Day-28 to Day-1)

At the start of Screening, the study will be discussed with the patient, and a patient wishing to participate must give written consent prior to any study-related procedures or change in treatment. The patient must also give written authorization regarding privacy requirements prior to any study-related procedures or change in treatment.

After informed consent is obtained, prospective patients will be evaluated for entry into the study according to inclusion and exclusion criteria (Section 4.1 and 4.2). Each patient who receives study treatment will be assigned a patient number that will be used on patient documentation throughout the study.

The patient should be instructed to fast (no food or drink other than water) before this clinic visit (at least 8 hours).

The following Screening procedures will be performed:

- Record medical history
- In patients with schizophrenia, conduct MINI
- In patients with bipolar disorder, conduct DSM-5 diagnostic assessment
- Record prior and concomitant medications
- Record demographic information
- Perform urine drug test
- Perform placebo tablet swallow assessment
- Measure height and body weight
- Measure waist-to-hip ratio
- Perform physical examination
- Record vital signs (including orthostatic vital signs)
- Perform 12-lead resting ECG (in triplicate)
- Conduct psychological assessments:
  - In patients with schizophrenia: C-SSRS, CGI, and BPRS
  - In patients with bipolar disorder: C-SSRS, CGI, YMRS, and MADRS-SIGMA
- Perform laboratory tests:
  - Hematology with platelet and white blood cell count (WBC) differential
  - Chemistry panel (fasting)
  - Lipid panel (fasting)
  - HbA1c
  - Serum pregnancy test (women of child-bearing potential)

  - FSH test (only for women who have medically confirmed ovarian failure or are postmenopausal)
  - Hepatitis B screening
  - Hepatitis C screening
  - Thyroid-stimulating hormone (TSH)
  - Free thyroxine (T4)

## 7.2 Baseline (Day 1)

The patient should be instructed to fast (no food or drink other than water) before this clinic visit (at least 8 hours). The following procedures will be performed for the baseline assessment at Day 1:

- Confirm informed consent was obtained
- Confirm patient eligibility (see Section 4.1 and 4.2 for inclusion and exclusion criteria)
- Confirm medical and medication history
- Record concomitant medications
- Perform urine drug test
- Measure body weight
- Measure waist-to-hip ratio
- Perform physical examination
- Record vital signs (including orthostatic vital signs)
- Perform 12-lead resting ECG (in triplicate) before dosing and 2 hr ±15 min after dosing
- Perform laboratory tests:
  - Hematology with platelet and WBC differential
  - Chemistry panel (fasting)
  - Lipid panel (fasting)
  - HbA1c
  - ACTH (morning–8 AM)
  - Serum insulin (fasting)
  - Plasma glucose (fasting)
  - Serum cortisol (morning–8 AM)
  - TSH
  - T4
  - Urine pregnancy test (women of child-bearing potential); if urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test
- Conduct psychological assessments:
  - In patients with schizophrenia: C-SSRS, CGI, and BPRS
  - In patients with bipolar disorder: C-SSRS, CGI, YMRS, and MADRS-SIGMA
- Glucocorticoid receptor activity marker
- Provide dietary and exercise counseling
- Record any AEs
- Perform study randomization

- Dispense study tablets; patient will take their first dose of study treatment in the clinic at this visit after clinic assessments
- Provide the patient with dose diary

## 7.3 Treatment Period

At all clinic visits during the Treatment Period, the following will be performed:

- Record any AEs
- Record concomitant medications
- Perform urine pregnancy test (women of child-bearing potential); if urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test
- Perform physical examination
- Measure body weight
- Record waist-to-hip ratio
- Record vital signs (including orthostatic vital signs)
- Perform 12-lead resting ECG (in triplicate)
- Conduct psychological assessments:
  - In patients with schizophrenia: C-SSRS, CGI, and BPRS
  - In patients with bipolar disorder: C-SSRS, CGI, YMRS, and MADRS-SIGMA

In addition, assessments will be performed at specific visits of the Treatment Period as indicated in the following sections.

### 7.3.1 Week 1: Study Day 8 (±2 Days)

- Perform assessments listed in Section 7.3
- Dispense study tablets
- Perform laboratory tests:
  - Chemistry panel
  - Hematology with platelet and WBC differential
- Record unused study tablets brought back by the patient
- Evaluate study treatment adherence based on returned dose diary and counting unused study tablets

### 7.3.2 Week 2: Study Day 15 (±2 Days)

- Perform assessments listed in Section 7.3
- Dispense study tablets
- Perform laboratory tests:
  - Chemistry panel
- Record unused study tablets brought back by the patient
- Evaluate study treatment adherence based on returned dose diary and counting unused study tablets

### 7.3.3 Week 4: Study Day 29 (±2 Days)

- Perform assessments listed in Section 7.3
- Dispense study tablets
- Perform laboratory tests:
  - Chemistry panel
  - Hematology with platelet and WBC differential
  - Lipid panel
  - ACTH (morning–8 AM)
  - Serum cortisol (morning–8 AM)
- Record unused study tablets brought back by the patient
- Evaluate study treatment adherence based on returned dose diary and counting unused study tablets

**For patients who consent to participate in the PK substudy only:**

Patients in the PK substudy will be required to take their dose of study treatment both the day prior and the day of their Week 4 visit in the clinic (witnessed dosing). Blood samples will be collected at the time points specified in the PK plan outlined in the study manual.

### 7.3.4 Week 6: Study Day 43 (±2 Days)

- Perform assessments listed in Section 7.3
- Dispense study tablets
- Perform laboratory tests:
  - Chemistry panel
- Record unused study tablets brought back by the patient
- Evaluate study treatment adherence based on returned dose diary and counting unused study tablets
- Provide a refresher on dietary and exercise counseling on weight loss

### 7.3.5 Week 8: Study Day 57 (±2 Days)

- Perform assessments listed in Section 7.3
- Dispense study tablets
- Perform laboratory tests:
  - Chemistry panel
  - Hematology with platelet and WBC differential
  - Lipid panel
- Record unused study tablets brought back by the patient
- Evaluate study treatment adherence based on returned dose diary and counting unused study tablets

### 7.3.6 Week 10: Study Day 71 (±2 Days)

- Perform assessments listed in Section 7.3
- Dispense study tablets

- Perform laboratory tests:
  - Chemistry panel
- Record unused study tablets brought back by the patient
- Evaluate study treatment adherence based on returned dose diary and counting unused study tablets

### 7.3.7 Week 12: Study Day 85 (±2 Days)

Patients should be instructed to fast before this clinic visit (i.e., no food or drink other than water for at least 8 hours).

- Perform assessments listed in Section 7.3
- Perform laboratory tests:
  - Chemistry panel (fasting)
  - Hematology with platelet and WBC differential
  - Lipid panel (fasting)
  - Serum insulin (fasting)
  - Plasma glucose (fasting)
  - ACTH (morning–8 AM)
  - Serum cortisol (morning–8 AM)
  - TSH
  - Free T4
  - HbA1c
- Record unused study tablets returned by the patient
- Evaluate study treatment adherence based on returned dose diary and counting unused study tablets
- Glucocorticoid receptor activity marker

## 7.4 Early Termination Visit (In-Clinic Visit)

Patients who discontinue the study drug before the end of the Treatment Period (12 weeks) will be asked to complete an ET visit at the time of the last dose of study drug (or soon thereafter). They should be instructed to fast before coming to the ET clinic visit (i.e., no food or drink other than water for at least 8 hours).

The following assessments should be performed during the ET visit:

- Record any AEs
- Record concomitant medications
- Record unused study tablets returned by the patient
- Evaluate study treatment adherence based on dose diary and pill counting
- Perform physical examination
- Measure body weight
- Record waist-to-hip ratio
- Record vital signs (including orthostatic vital signs)
- Perform 12-lead resting ECG (in triplicate)

- Perform laboratory tests:
  - Urine pregnancy test (women of child-bearing potential); if urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test
  - Hematology with platelet and WBC differential
  - Chemistry panel (fasting)
  - Lipid panel (fasting)
  - HbA1c
  - Serum insulin (fasting)
  - Plasma glucose (fasting)
  - TSH
  - Free T4
  - ACTH (morning–8 AM)
  - Serum cortisol (morning–8 AM)
- Conduct psychological assessments:
  - In patients with schizophrenia: C-SSRS, CGI, and BPRS
  - In patients with bipolar disorder: C-SSRS, CGI, YMRS, and MADRS-SIGMA
- Glucocorticoid receptor activity marker

### 7.5 Follow-Up Visit (In-Clinic Visit; 28±5 Days after Last Dose of Study Drug)

For patients who complete 12 weeks of treatment or for patients who discontinue early from the study drug, the Follow-Up visit will be conducted 28±5 days after their last dose of study drug. The following assessments should be performed during the end-of-study Follow-up visit:

- Record any AEs
- Record concomitant medications
- Perform physical examination
- Measure body weight
- Record waist-to-hip ratio
- Record vital signs (including orthostatic vital signs)
- Perform 12-lead resting ECG (in triplicate)
- Perform laboratory tests:
  - Urine pregnancy test (women of child-bearing potential); if urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test
  - Hematology with platelet and WBC differential
  - Chemistry panel
  - Lipid panel
- Conduct psychological assessments:
  - In patients with schizophrenia: C-SSRS, CGI, and BPRS
  - In patients with bipolar disorder: C-SSRS, CGI, YMRS, and MADRS-SIGMA

## 7.6 Unscheduled Visits

As appropriate, assessments deemed clinically necessary by the Investigator may be done at unscheduled visits.

# 8 SAFETY EVENT DOCUMENTATION AND REPORTING

## 8.1 Investigator's Responsibilities

Investigators are responsible for monitoring the safety of patients who have entered this study and for providing appropriate medical care. By exercising appropriate healthcare options, the Investigator remains responsible for managing AEs. Duration of follow-up and requirements for *immediate* SAE reporting (within 24 hours of the event) are described below.

## 8.2 Monitoring Safety Data During the Study

Safety results collected during the study (e.g., AEs, laboratory test results, and physical findings) will be monitored on an ongoing basis by the Corcept Medical Monitor and Investigator. In addition, an IDMC will be established to conduct periodic reviews of data to ensure the safety of patients (Section 5.9). All abnormal lab, ECG, and exam findings will be assessed for clinical significance. The use of CTCAE severity grading will be implemented for systematically and consistently evaluating abnormal labs, ECG and vitals findings. All grade 3 and above findings will immediately be reported to Corcept's Medical Monitor within 24 hours.

In addition, an IDMC will conduct periodic reviews of data to ensure the safety of patients (see Section 5.9).

## 8.3 Definition of an Adverse Event

An AE is any untoward medical occurrence in a study patient administered a pharmaceutical product, which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product that emerges or worsens relative to the patient's pretreatment baseline, whether or not it is considered to be related to the investigational product.

Illnesses present before the patient signs the ICF are considered pre-existing conditions and are documented on the medical history eCRF. Pre-existing conditions that worsen during the study are entered on the AE eCRF.

## 8.4 Definition of a Serious Adverse Event

An SAE is any AE that meets any of the following criteria:

- Results in death (i.e., the AE caused or led to the fatality).
- Is life-threatening (i.e., the AE refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).
- Requires hospitalization or prolongation of existing hospitalization (i.e., hospitalizations for scheduled treatments and elective medical/surgical procedures are not SAEs by this criterion).
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial reduction of the patient's ability to perform activities of daily living).

- Results in a congenital anomaly or birth defect (i.e., an adverse finding in a child or fetus of a patient exposed to the study medication before conception or during pregnancy).
- Involves other medically important conditions (i.e., the AE does not meet any of the above serious criteria but based on appropriate medical judgment, may jeopardize the patient or require medical or surgical intervention to prevent one of the serious outcomes listed in these criteria).

## 8.5 Expectedness

An SAE is considered unexpected if not reported in the IB or if the event is of greater severity or frequency than described in the IB.

## 8.6 Clinical Significance

The Investigator (or medically qualified designee) is responsible for determining whether an AE is clinically significant for the patient. Clinical significance will be documented in the patient's medical records with the AE information.

## 8.7 Clinical Laboratory Adverse Events

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

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

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

Patients with a clinically significant out-of-range laboratory value will be followed until the laboratory value returns to normal, or the patient's baseline value, or the value becomes medically stable, or the patient is deemed by the Investigator to be lost to follow-up. The Investigator will treat the patient as medically required at appropriate intervals until this occurs. The Investigator should report any Grade 3 or 4 laboratory abnormalities to Corcept.

## 8.8 Documentation of Adverse Events

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

Collection of AEs will start immediately following signing of the ICF and will continue throughout the study as noted in the SoA (Appendix A). Illnesses present before the patient signs the ICF are considered pre-existing conditions and are to be documented on the medical history eCRF. Pre-existing conditions that worsen during the study are entered on the AE eCRF. Adverse events that occur after start of study treatment after randomization to miricorilant or placebo and up to and including 28 days after administration of the last dose of miricorilant or placebo will be considered TEAEs.

All AEs will be documented on the AE eCRF and in the patient's medical record. The following attributes must be assigned: (1) description, (2) dates of onset and resolution, (3) severity (see

Section 8.9.1), (4) relationship to the study treatment (see Section 8.9.2), (5) seriousness criteria if applicable (see Section 8.4), and (6) action taken. The Investigator will actively solicit this information and assess the AEs in terms of severity and relationship to each study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a unifying diagnosis whenever possible, rather than individual underlying signs and symptoms. The Investigator will treat the patient as medically required until the AE either resolves or becomes medically stable. This treatment may extend beyond the duration of the study. The Investigator will record treatment and medications required for treatment on the appropriate eCRF(s).

In the event that a patient is withdrawn from the study because of an AE, the event must be recorded on the Termination eCRF as the reason for discontinuation.

All AEs considered to be related (see Section 8.9.2) to study treatment and all SAEs will be followed until resolved or until a stable status has been achieved.

All SAEs that are study treatment-related and unexpected (not reported in the IB or if the event is of greater severity or frequency than that described in the IB) must be reported to the governing IRB as required by the IRB, local regulations, and the governing health authorities.

## 8.9 Adverse Event Classification

### 8.9.1 Intensity Grades of Adverse Events

The seriousness of an AE should not be confused with its severity. To describe the maximum severity of the AE on the AE eCRF, the Investigator will use the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 5.0 (NCI 2017). For events not listed in the NCI-CTCAE, the definitions from the NCI-CTCAE provided in Table 5 should be used to evaluate the grade of severity for the AE.

**Table 5 Adverse Event Grades Based on the Common Terminology Criteria for Adverse Events**

| Grade | Description |
|---|---|
| 1 | **Mild:** asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated |
| 2 | **Moderate:** minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (e.g., preparing meals, shopping for groceries or clothes, using the telephone, and managing money) |
| 3 | **Severe**: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting selfcare activities of daily living (e.g., bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden) |
| 4 | **Life-threatening:** Life-threatening consequences; urgent intervention indicated |
| 5 | **Death:** Death related to AE |

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

### 8.9.2 Relationship of Adverse Event to Study Drug or Procedure

The Investigator responsible for the patient's care (or qualified designee) will assess causality of AEs and SAEs based on the causal attribution guidance in Table 6. The Investigator's assessment of causality must be provided for all AEs (serious and nonserious).

**Table 6 Causal Attribution Guidance for Adverse Events**

| | |
|---|---|
| Not related to study treatment | An AE that is judged to be clearly due only to extraneous causes such as diseases, environment, and the like or for which it is temporally implausible to be related to use of the study treatment. The cause must be noted on the AE eCRF. |
| Possibly related to study treatment | An AE that might be due to the use of the study treatment. The relationship in time is reasonable; therefore, a causal relationship cannot be excluded. An alternative explanation is inconclusive, e.g., concomitant drug (s), concurrent disease (s). |
| Probably related to study treatment | An AE that might be due to the use of the study treatment. The relationship in time is suggestive. An alternative explanation is less likely, e.g., concomitant drug(s) or concurrent disease(s). |

## 8.10 Procedures for Reporting a Serious Adverse Event

Any SAE occurring from the time of informed consent and for ≤28 days after the last dose of study treatment *must be reported within 24 hours* to the Corcept Medical Monitor and recorded on the SAE Form. All patients with an SAE must be followed and the outcomes reported. The Investigator must supply Corcept and the IRB with any additional requested information (e.g., autopsy reports and terminal medical reports).

## 8.11 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

There are no disease-related events or disease-related outcomes that are considered as not qualifying as AEs or SAEs (i.e., all AEs and SAEs should be reported as indicated in Sections 8.8 and 8.10, respectively).

Deaths with an unknown cause should always be reported as an SAE, but every effort should be made to establish a cause of death.

## 8.12 Adverse Event Follow-Up

All AEs considered to be related to study treatment (see Section 8.9.2) and all SAEs will be followed until resolution, until deemed stable by the Investigator, or until the patient is deemed by the Investigator to be lost to follow-up.

## 8.13 Pregnancy

All pregnancies during the study and within 28 days of the last dose of the study treatment should be reported to Corcept; the outcomes of pregnancies should be reported to Corcept at the term of the gestational period.

### 8.13.1 Maternal Exposure

If a patient becomes pregnant during the study, study treatment should be discontinued immediately. Pregnancy itself is not regarded as an AE unless there is a suspicion that the study treatment may have interfered with the effectiveness of a contraceptive medication.

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

Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed and documented for up to 2 months after the completion of pregnancy even if the patient discontinued the study.

The designated Sponsor representative works with the Investigator to ensure that all relevant information is provided to the Corcept Patient Safety data entry site within 24 hours for SAEs (see Section 8.10) and within 28 days for all other pregnancies. The same timelines apply when outcome information is available.

### 8.13.2 Paternal Exposure

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed and documented, if possible. To capture information about a pregnancy from the partner of a male patient, the Investigator or designee must first obtain the consent of the male patient's partner; the male patient should not be asked to provide this information. A consent form specific to this situation must be used. The outcome of any conception occurring from the date of the first dose until 28 days after the last dose should be followed and documented for up to 2 months after the completion of pregnancy.

## 8.14 Treatment of Overdose

There is currently no experience with overdose of miricorilant. For monitoring symptoms of excessive GR and MR antagonism, refer to Section 5.3.3.

## 8.15 Emergency Sponsor Contact

In a medical emergency (i.e., an event that requires immediate attention regarding the treatment of a patient, operation of the clinical study, and/or the use of investigational product), study site personnel will apply appropriate medical intervention according to current standards of care and contact the Corcept Medical Monitor.

# 9 STATISTICAL METHODS

Detailed procedures for statistical analyses to be performed for this study will be provided in a separate Statistical Analysis Plan (SAP) that will be finalized before database lock.

## 9.1 Analysis Populations

The analysis populations are defined in Table 7.

**Table 7 Definitions of Analysis Populations**

| Population | Description |
|---|---|
| All Enrolled | All patients who meet the study enrollment criteria. |
| Safety Population | All patients who receive at least 1 dose of study medication. |
| Intent-to-Treat (ITT) Population | All patients who receive at least 1 dose of study medication. |
| Efficacy Evaluable (EE) Population | All patients who receive ≥4 weeks of study medication and have baseline and ≥1 body weight measurement taken on or after Week 4. |
| PK Population | All patients who have evaluable PK data. |

Summaries of demographics and baseline conditions will be done for the All Enrolled, Safety and Efficacy Evaluable (EE) Populations. Analysis of safety data will be performed on the Safety Population. Analysis of efficacy data will be performed on the EE Population. Sensitivity analyses of the primary and other key endpoints will also be performed on the Intent-to-Treat (ITT) Population.

Pharmacokinetic analyses will be based on the PK Population. Prematurely discontinued patients and patients with missing sample concentrations will be included in the PK analyses, provided their PK parameters can be adequately characterized based on the remaining data.

All summaries will be presented by assigned treatment group. In addition, data will be tabulated for all patients combined. All relevant data collected on the 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, standard deviation (SD), median, minimum, and maximum values. Categorical variables will be summarized by the number and percentage of patients in each category.

Predose measurements on Day 1 will be considered the baseline values. If a Day 1 predose value is not available, the screening measurement may be used as the baseline value.

## 9.2 Hypothesis Testing

All statistical hypotheses will be tested at a 2-sided $\alpha$=0.05 significance level unless otherwise specified.

## 9.3 Sample Size Calculation

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 $\alpha$=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 a 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 (active risperidone metabolite), 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 antipsychotic medication.

## 9.4 Analysis Plan

### 9.4.1 Patient Disposition

Patient disposition summaries will include the number of enrolled patients, the number of enrolled patients in each analysis population, the number of patients completing the study per protocol, and the number of patients terminating the study early by the primary reason for discontinuation.

### 9.4.2 Demographic and Baseline Data

Demographic and baseline data will include frequency and percentages for categorical variables, and mean, standard deviation, median, minimum, and maximum for continuous variables. Demographic and baseline characteristics will be summarized by treatment group and overall.

### 9.4.3 Concomitant Medications

Verbatim terms on eCRFs will be mapped to Anatomical Therapeutic Chemical class and Generic Drug Names using the most current version of the World Health Organization Drug Dictionary. Concomitant medications will be summarized for all treatment patients by treatment group and overall.

### 9.4.4 Safety Analyses

Adverse events will be mapped to system organ classes and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs will be summarized

overall and displayed by system organ class and preferred term, as well as by severity, seriousness, and relationship to the study treatment. Serious AEs and AEs that lead to study treatment discontinuation or withdrawal from the study will be listed by individual patient.

Clinical laboratory test results (chemistry, hematology, and coagulation), vital sign measurements, physical examination findings, and ECG results will be summarized by visit using descriptive statistics. Shift tables will be constructed that describe changes from baseline in clinical laboratory values.

### 9.4.5 Efficacy Analyses

Efficacy analyses will be performed on the EE Population. Sensitivity analyses of the primary and other key endpoints will be performed on the ITT Population (see Table 7 for definitions of analysis populations).

#### 9.4.5.1 Primary Efficacy Analysis

The primary efficacy endpoint is the change in body weight from baseline to Week 12. All values for body weight will be used in the analysis. For patients who discontinue treatment prior to Week 12 and do not have the Week 12 body weight available, a retrieved dropout approach will be used. The primary endpoint will be assessed using a mixed-effect model with repeated measures (MMRM) with change in body weight at each visit as the outcome variable; baseline body weight and antipsychotic medication (stratification factor) as covariates; and randomized treatment (600 mg miricorilant or placebo), visit, and treatment-by-visit interaction as fixed effects. The difference in body weight change between miricorilant and placebo will be estimated from the model along with its 95% confidence interval (CI).

#### 9.4.5.2 Sensitivity Analysis of Primary Endpoint

The MMRM used to assess the primary endpoint will be rerun as a sensitivity analysis using the ITT Population in place of the EE Population.

#### 9.4.5.3 Secondary Efficacy Analyses

The secondary efficacy endpoints are defined in Section 3.2.3.

The percentage of patients in each treatment group who lose ≥5% of their baseline body weight will be presented along with its 95% CI. In addition, a logistic regression model with baseline body weight and stratification factor as covariates will be used to compare miricorilant to placebo.

HOMA-IR will be calculated using the approximate formula (Matthews et al. 1985):

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

HOMA-IR and waist-to-hip ratio will be analyzed using similar models as the primary analysis of weight change. Both HOMA-IR and waist-to-hip ratio may be log-transformed prior to analysis. Model estimates derived from log-transformed data will be back-transformed to the original scale for presentation of the treatment effect of miricorilant compared to placebo. For patients who discontinue treatment prior to Week 12 and do not have the Week 12 HOMA-IR or

waist-to-hip ratio available, a retrieved dropout approach will be used similar to the primary efficacy analysis.

### 9.4.6 Pharmacokinetic Analysis

The PK variables for analysis are listed in Table 8; details of the PK analyses will be described in a PK analysis plan finalized before database lock.

The PK data obtained from the PK substudy, including the PK parameters of miricorilant estimated by noncompartmental methods, will be summarized descriptively. The 95% CIs for the PK parameters will be presented. Additionally, plasma concentrations of miricorilant will be plotted over time.

**Table 8 Pharmacokinetic Variables for Analysis**

| | |
|---|---|
| $\lambda_z$ | apparent terminal rate constant |
| AUC | area under the concentration-time curve |
| $AUC_{last}$ | AUC values from time 0 to time of last measurable concentration |
| $AUC_{tau}$ | AUC over the dosing interval |
| $C_{max}$ | maximum concentration over the dosing interval |
| $C_{tau}$ | concentration at the end of the dosing interval |
| $t_{1/2}$ | apparent terminal elimination half-life |
| $t_{last}$ | time of the last quantifiable concentration |
| $T_{max}$ | time to maximum concentration |

### 9.4.7 Exploratory Analysis

Analyses of continuous endpoints, such as the change in BPRS, CGI, MADRS-SIGMA, YMRS, ACTH, and serum cortisol from baseline to Week 12 will be analyzed using similar models as the primary analysis of body weight change. C-SSRS results will be summarized descriptively. Changes in HbA1c and fasting blood glucose within patients with diabetes will employ pairwise Wilcoxon rank-sum tests to compare treatment groups. A similar strategy will be used to compare groups on the change from baseline in blood pressure among patients with high blood pressure.

Exploratory analyses will be described in the SAP finalized before database lock.

### 9.4.8 Pharmacogenetic Analysis

Not applicable.

### 9.4.9 Interim Analysis

Not applicable.

# 10 ETHICAL AND LEGAL CONSIDERATIONS

## 10.1 Compliance with IRB Regulations

This study is to be conducted in accordance with IRB regulations (US 21 CFR Part 56.103) and applicable local regulations. The protocol, ICFs, recruitment materials, and all patient materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any patient is enrolled. The Investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. The protocol must be re-approved by the IRB on receipt of amendments and annually, as local regulations require.

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

Corcept is to be notified immediately if the responsible IRB has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB correspondence with the Investigator should be provided to Corcept.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB according to local regulations and guidelines.

## 10.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP and applicable regulatory requirements.

The Investigator will ensure that the study procedures outlined in this protocol will be conducted in accordance with applicable country and local regulations.

## 10.3 Protection of Human Patients

### 10.3.1 Compliance with Informed Consent Regulations

Written informed consent is to be obtained from each patient before enrollment into the study.

The Investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

- The ICF will contain all of the elements required by ICH guidelines for GCP and any additional elements required by local regulations.
- The ICF must include information about the possible retention of biological samples at the conclusion of this study; with the patient's permission, samples may be retained for future determination of active metabolite concentrations and possible biomarkers related to drug response.
- The patient's signed and dated ICF must be obtained before conducting any study procedures.

- The ICF must include information about the possible retention of biological samples at the conclusion of this study; with the patient's permission, blood, plasma, serum and tissue samples may be obtained for future analysis to help identify biomarkers of disease or miricorilant treatment.

The Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient.

### 10.3.2 Patient Confidentiality

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

### 10.3.3 Patient Privacy

The Investigator or designee must explain to each patient, before enrollment into the study, that for evaluation of study results, the patient's protected health information obtained during the study may be shared with Corcept, regulatory agencies, and IRB. It is the Investigator's (or designee's) responsibility to obtain written permission to use protected health information per country-specific regulations from each patient. If permission to use protected health information is withdrawn, it is the Investigator's responsibility to obtain a written request, to ensure that no further data will be collected from the patient, and the patient will be removed from the study.

Written authorization is to be obtained from each patient before enrollment into the study in accordance with the applicable privacy requirements.

# 11 ADMINISTRATIVE CONSIDERATIONS

## 11.1 Study Monitoring

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

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

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

## 11.2 Quality Management

Study sites, the study database, and study documentation will be monitored regularly and may be subject to a quality assurance audit during the study by Corcept or its designee on behalf of Corcept. In addition, inspections may be conducted by regulatory agencies at their discretion.

Quality control procedures will be implemented beginning with the data entry system and data quality control checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., GLP and Good Manufacturing Practices).

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

## 11.3 Documentation

### 11.3.1 Case Report Forms and Study Records

The Investigator must generate and maintain complete, adequate, accurate, reliable, and consistent records to enable full documentation of study conduct. Study data will be captured in an EDC system on eCRFs. Investigators must retain all original source documents, and Corcept or its designee will notify Investigators in writing when the trial-related records are no longer needed.

### 11.3.2 Access to Source Documentation

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

The Investigator should contact Corcept immediately if contacted by a regulatory agency regarding an inspection.

### 11.3.3 Source Documents

Source documents provide all original records of clinical findings, observations, or other information from a clinical trial necessary for the reconstruction and evaluation of the trial (e.g., a patient's medical records, hospital charts, and clinic charts; the Investigator's patient study files; results of diagnostic tests, including laboratory tests and ECGs). All source data should be attributable, legible, contemporaneous, original, accurate, and completed. Changes to source data should be traceable, should not obscure the original entry, and should be explained, if necessary.

Investigators must retain all original source documents. The Sponsor or its designee will notify Investigators in writing when the trial-related records are no longer needed.

### 11.3.4 Study Files and Retention of Study Records

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified.

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of Corcept, if applicable. It is the responsibility of Corcept to inform the Investigator when these documents no longer need to be retained.

Patient identification codes (patient names and corresponding study numbers) will be retained for this same period of time. These documents may be transferred to another responsible party, acceptable to Corcept, who agrees to abide by the retention policies. Written notification of transfer must be submitted to Corcept. The Investigator or designee must contact Corcept before disposing of any study records.

## 11.4 Long-Term Retention of Biological Samples

No samples will be retained long term (ie, beyond clinical study report) without prior written consent of the subject and IRB or IEC approval. All long-term retention samples will be retained by Corcept or designee. The long-term retention samples will be coded to allow de-identification according to applicable regulatory guidelines.

After conclusion of this study, the long-term samples will be held for a period up to 10 years, after which they will be destroyed. During the conduct of the study, an individual subject can choose to withdraw consent to have his or her samples stored for future research; however, withdrawal of consent with regard to biological sample storage will not be possible after the study is completed.

## 11.5 Clinical Supplies

### 11.5.1 Inventory, Reconciliation, Return, and Disposition of Clinical Supplies

All study drug and related materials should be stored, inventoried, reconciled, and destroyed or returned according to applicable state and federal regulations and study procedures. Storage of study drug is described in Table 1.

### 11.5.2 Clinical-Supply Inventory

A detailed inventory must be completed for all study drug. The study drug is to be used in accordance with the protocol by patients who are under the direct supervision of an Investigator. The study drug must be dispensed only by an appropriately qualified person to patients in the study.

Unused study drug must be kept in a secure location for accountability and reconciliation by the study monitor. The Investigator or designee must provide an explanation for any destroyed or missing study drug or study materials.

The Investigator or designee is responsible for maintaining accurate records (including dates and quantities) of study drug(s) received, patients to whom study drug is dispensed (patient-by-patient dose-specific accounting), and study drug lost or accidentally or deliberately destroyed. The Investigator or designee must retain all unused or expired study supplies until the study monitor (on-site clinical research associate) has confirmed the accountability data and Corcept has approved return or destruction.

### 11.5.3 Return or Disposal of Study Drug and/or Supplies

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

Unused study drug may be destroyed on site, per the site's standard operating procedures, but only after Sponsor has granted approval for drug destruction. The monitor must account for all study drug in a formal reconciliation process, before study-drug destruction. All study drug destroyed on site must be documented.

Documentation must be provided to Corcept and retained in the Investigator study files. If a site is unable to destroy study drug appropriately, the site can return unused study drug to Corcept

upon request. The return of study drug or study drug materials must be accounted for on a Study Drug Return Form provided by Corcept.

## 11.6 Drug Accountability

It is the responsibility of the Investigator to maintain drug accountability at the study site and ensure that a current record of investigational product disposition is maintained. It is the responsibility of the Investigator to ensure that the investigational product is used only in accordance with the approved protocol. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient dispensing records, and returned or destroyed study product. Dispensing records will document quantities received from Corcept (or Corcept's designee) and quantities dispensed to patients, including lot number, date dispensed, patient identifier number, patient initials, and the initials of the person dispensing the drug. At the end of the study, after final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused investigational medicinal product supplies, including empty containers, according to standard procedures.

## 11.7 Post-trial Care

There is no provision for continuation of the investigational drug beyond the end of study treatment. Corcept will work with the Investigator to ensure that study participants continue to receive appropriate care, which may include referral to an ongoing clinical trial or another investigational treatment or may involve transition to medical management outside the research context.

## 11.8 Noncompliance with the Protocol

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

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

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

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

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

## 11.9 Financial Disclosure

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

## 11.10 Publication and Disclosure Policy

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

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

Corcept will comply with the requirements for publication of study results and determination of authorship in accordance with standard editorial and ethical practice and with the International Committee of Medical Journal Editors requirements.

## 11.11 Final Report Signature

Corcept's responsible Medical Officer will approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

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# 13 APPENDICES

## Appendix A: Schedule(s) of Assessments

### Table 9 Schedule of Clinical Assessments and Procedures

| Assessment | Screening Days−28 to−1 | Baseline Day 1 | Treatment Period | | | | | | | ET [a] | Follow-up 28±5 days after last dose of study drug |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Week 1 Day 8±2 days | Week 2 Day 15±2 days | Week 4 Day 29±2 days | Week 6 Day 43±2 days | Week 8 Day 57±2 days | Week 10 Day 71±2 days | Week 12 Day 85±2 days | | |
| Informed consent [b] | X | | | | | | | | | | |
| Inclusion/exclusion criteria [b] | X | | | | | | | | | | |
| Medical history and prior medications [c] | X | | | | | | | | | | |
| Swallow assessment | X | | | | | | | | | | |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X | X |
| Randomization | | X | | | | | | | | | |
| Record AEs [c] | | X | X | X | X | X | X | X | X | X | X |
| Demographics | X | | | | | | | | | | |
| Serum pregnancy test [d] | X | | | | | | | | | | |
| Urine pregnancy test [d] | | X | X | X | X | X | X | X | X | X | X |
| FSH test [e] | X | | | | | | | | | | |
| Urine drug test | X | X | | | | | | | | | |
| Diet and exercise counseling | | X | | | | X | | | | | |
| Physical examination [f] | X | X | X | X | X | X | X | X | X | X | X |
| Body weight | X | X | X | X | X | X | X | X | X | X | X |
| Height | X | | | | | | | | | | |
| Vital signs (including orthostatic vital signs) | X | X | X | X | X | X | X | X | X | X | X |
| 12-lead resting ECG (in triplicate) [g] | X | X | X | X | X | X | X | X | X | X | X |
| Waist-to-hip ratio | X | X | X | X | X | X | X | X | X | X | X |
| Dispensing of study treatment (tablets) | | X | X | X | X | X | X | X | | | |
| Accounting of unused tablets | | | X | X | X | X | X | X | X | X | |
| Dose diary provided | | X | | | | | | | | | |
| Dose diary (assessed and returned to patient) | | | X | X | X | X | X | X | X | X | |

| Assessment | Screening Days−28 to−1 | Baseline Day 1 | Treatment Period | | | | | | | ET [a] | Follow-up 28±5 days after last dose of study drug |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Week 1 Day 8±2 days | Week 2 Day 15±2 days | Week 4 Day 29±2 days | Week 6 Day 43±2 days | Week 8 Day 57±2 days | Week 10 Day 71±2 days | Week 12 Day 85±2 days | | |
| Virus screen (HCV, HBV) | X | | | | | | | | | | |
| Hematology with platelet and WBC differential | X | X | X | | X | | X | | X | X | X |
| Chemistry [h] | X | X | X | X | X | X | X | X | X | X | X |
| Lipid panel [i] | X | X | | | X | | X | | X | X | X |
| HbA1c | X | X | | | | | | | X | X | |
| Serum insulin, fasting | | X | | | | | | | X | X | |
| Plasma glucose, fasting | | X | | | | | | | X | X | |
| TSH | X | X | | | | | | | X | X | |
| Free T4 | X | X | | | | | | | X | X | |
| ACTH (morning–8 AM) | | X | | | X | | | | X | X | |
| Serum cortisol (morning–8 AM) | | X | | | X | | | | X | X | |
| Glucocorticoid receptor activity marker | | X | | | | | | | X | X | |
| MINI | X | | | | | | | | | | |
| DSM-5 bipolar disorder assessment | X | | | | | | | | | | |
| BPRS | X | X | X | X | X | X | X | X | X | X | X |
| C-SSRS | X | X | X | X | X | X | X | X | X | X | X |
| CGI | X | X | X | X | X | X | X | X | X | X | X |
| YMRS | X | X | X | X | X | X | X | X | X | X | X |
| MADRS-SIGMA | X | X | X | X | X | X | X | X | X | X | X |
| PK substudy [j] | | | | | X | | | | | | |

Abbreviations: ACTH, adrenocorticotropic hormone; AE, adverse event; BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impression, C-SSRS, Columbia-Suicide Severity Rating Scale; DSM-5, American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders; ECG, electrocardiogram; ET, early termination; FSH, follicle-stimulating hormone; HbA1c, glycated hemoglobin; ICF, informed consent form; MADRS-SIGMA, Montgomery-Åsberg Depression Rating Scale; MINI, Mini International Neuropsychiatric Interview; PK, pharmacokinetic; T4, thyroxine; TSH, thyroid-stimulating hormone; WBC, white blood cell (count); YMRS. Young Mania Rating Scale.

a. Patients who discontinue the study drug before the end of the Treatment Period will be asked to complete the ET visit at the time of the last dose of study drug (or soon thereafter); Follow-Up visit will be conducted 28±5 days after the last dose of study drug.

b. Confirm informed consent was obtained and patient meets inclusion/exclusion criteria prior to randomization at Baseline Day 1 Visit.

c. Illnesses present before the patient signs the ICF are considered pre-existing conditions and are to be documented on the medical history eCRF. Illness/events that occur after patient signs the consent and pre-existing conditions that worsen will be recorded as AEs.
d. Serum and urine pregnancy tests will be completed on all women of child-bearing potential. If urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test.
e. An FSH test will be completed on women who have medically confirmed ovarian failure or are postmenopausal. Menopause is defined as cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause, and an FSH level within the laboratory's reference range for a postmenopausal woman.
f. All physical examinations should include a basic neurological exam.
g. At Baseline, the 12-lead resting ECG (in triplicate) will be performed both before dosing and 2 hr ±15 min after dosing.
h. Fasting chemistry panels will occur on Screening, Baseline, Week 12 and ET. All other chemistry panels will be done non-fasting
i. Lipid panel to include cholesterol, triglycerides, direct low-density lipoprotein (LDL), very-low density LDL (VLDL) and high-density lipoprotein (HDL). Fasting lipid panels will occur on Screening, Baseline, Week 12, and ET. All other lipid panels will be done non-fasting.
j. Blood samples will only be collected from patients who consent to participate in the PK substudy, at the time points specified in the PK plan outlined in the study manual. Note: Patients will be required to take their dose of study treatment both the day prior and the day of their Week 4 visit in the clinic (witnessed dosing).

## Appendix B: Summary of Changes

Significant changes in Amendment 5 of the protocol dated 11 January 2022 compared with the Amendment 4 dated 03 August 2021 are summarized below with additional details in Table 10; deleted text is shown as a ~~strikethrough~~ and new text is shown in **bold**.

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

Significant revisions to the protocol include the following:

- Stopping criteria for study drug in case of suspected liver injury was modified per IDMC recommendations.
- Change in number of patients planned for the study.

## Table 10 Summary of Changes in Protocol CORT118335-876 Amendment 5

| Section | Summary of Change | Revisions |
|---|---|---|
| Global changes | Updated version and date of the protocol. | ~~Amendment 4~~**Amendment 5**<br>~~03 August 2021~~**11 January 2022** |
| Synopsis | Updated text in synopsis to align with changes in the protocol body. | -- |
| 1.4.2 Design Considerations | Modified the expected number of patients to be randomized in the study. | *Paragraph 1:*<br>This is a Phase 2, randomized, double-blind, placebo-controlled study to evaluate the safety, efficacy, and PK of miricorilant. This study will be conducted in the USA, at approximately 35 sites, and will randomize approximately ~~100~~**70** patients with schizophrenia or bipolar disorder who have recent AIWG (see Section 4.1, exclusion criterion #6) in a 1:1 ratio to 600 mg miricorilant or placebo. |
| 3.1 Overall Design | Modified study design to align with changes to expected number of patients to be randomized. | CORT118335-876 Study Design (Figure 3) updated. |
| 3.3.1 Number of Patients | Modified the expected number of patients to be randomized in the study. | *Paragraph 1*:<br>Approximately ~~100~~ **70** patients will be randomized in this study, with a target of randomizing ~~50~~**35** patients in each treatment group: 600 mg miricorilant and placebo. See Section 9.3 for details regarding sample size calculation. See Section 4.5 for details regarding replacement of patients. |
| 5.3.3 Dose Interruption and/or Discontinuation: Special Safety Events | In Table 2, stopping criteria for study drug in case of suspected liver injury was modified per IDMC recommendations. | Table 2:<br>*Row 4:*<br>Suspected liver injury<br>Criteria: AST or ALT > 3 × ULN or total bilirubin > 2.0 × ULN while on study drug<br>Management:<br>• Repeat liver biochemistries (ALT, AST, alkaline phosphatase, total bilirubin) within 48 to 72 hours of results.<br>• Obtain a more detailed history of symptoms and prior or concurrent disease and a history of concomitant drug use (including<br>Study drug will be stopped if:<br>• ~~ALT or AST > 8 × ULN.~~<br>• ALT or AST > 5 × ULN ~~for more than 2 weeks~~.<br>• ALT or AST > 3 × ULN and (TBL >2 × ULN or INR >1.5).<br>• ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%). |

| Section | Summary of Change | Revisions |
|---|---|---|
| | | nonprescription medication and herbal and dietary supplement preparations).<br>• Obtain a history of exposure to environment chemical agents.<br>• Rule out other causes of liver disease.<br>• Obtain additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).<br>• Continue to monitor the liver biochemistry two or three times weekly but no less frequently than once weekly. Frequency can decrease to once a week or less if abnormalities stabilize, or study drug has been discontinued and the patient is asymptomatic.<br>• Consider a gastroenterology or hepatology consultation.<br>• During the period of close observation, study drug can be continued if desired at the discretion of Corcept Medical Monitor and Investigator unless one of the criteria for stopping study treatment are met. |
| 5.4.3 Prohibited Medications | Updated the list of prohibited medications to include inhaled corticosteroids. | The following medications are prohibited during treatment with miricorilant in this study:<br>….<br>*Bullet 6:*<br>• Systemic corticosteroids**, including inhaled corticosteroids** ~~[~~**(**with exception of temporary use for treatment of excessive GR antagonism~~]~~**)**, potent (group III) topical corticosteroids, and intra-articular corticosteroids |

| Section | Summary of Change | Revisions |
|---|---|---|
| 8.10 Procedures for Reporting a Serious Adverse Event | Text updated to remove reference to cover page with respect to the Medical Monitor. | Any SAE occurring from the time of informed consent and for ≤28 days after the last dose of study treatment must be reported within 24 hours to the Corcept Medical Monitor ~~listed on the cover page~~ and recorded on the SAE Form. All patients with an SAE must be followed and the outcomes reported. The Investigator must supply Corcept and the IRB with any additional requested information (e.g., autopsy reports and terminal medical reports). |
| 8.15 Emergency Sponsor Contact | Text updated to remove reference to cover page with respect to the Medical Monitor. | In a medical emergency (i.e., an event that requires immediate attention regarding the treatment of a patient, operation of the clinical study, and/or the use of investigational product), study site personnel will apply appropriate medical intervention according to current standards of care and contact the Corcept Medical Monitor listed ~~on the cover page~~. |
| 9.3 Sample Size Calculation | Updated text to reflect changes in sample size. | Approximately ~~100~~**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 ~~5~~**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 ~~conservative~~ SD of ~~6~~**4.5** kg is assumed here. Assuming a difference in body weight change between groups of ~~5~~**4** kg with an SD of ~~6~~**4.5** kg, and setting $\alpha$=0.05, ~~30~~**28** patients per group provides 90% power to detect a significant difference between active dose group and placebo after completing 12 weeks of treatment.<br>Allowing for ~~40~~**20**% dropouts increases the required sample size to ~~50~~**35** patients per group for a total of ~~100~~**70** patients in the trial.<br>With ~~50~~**35** patients receiving 600 mg miricorilant in the trial, there is a ~~92~~**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 ~~6.4~~**10**%.<br>Randomization will be stratified by the type of antipsychotic medication used [olanzapine, risperidone/paliperidone (active risperidone metabolite), quetiapine, aripiprazole, or other]. If at least ~~20~~**14** patients complete 12 weeks of treatment (~~10~~**7** patients treated with 600 mg miricorilant and ~~10~~**7** patients treated with placebo) in one of the allowed antipsychotic medications, this sample size provides ~~60~~**50**% power to detect a difference in body weight change of ~~5~~**4** kg between 600 mg miricorilant and placebo, at alpha=0.1 level for that antipsychotic medication. |