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

NCT Number: NCT04524403

Date: 09 June 2022

CLINICAL STUDY PROTOCOL CORT118335-877

Title	**A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Efficacy, and Pharmacokinetics of Miricorilant in Obese Adult Patients with Schizophrenia Taking Antipsychotic Medications (GRATITUDE II)**
Investigational Product	Miricorilant
Medical Monitor	[redacted]
Sponsor	Corcept Therapeutics Incorporated 149 Commonwealth Drive Menlo Park, California 94025 US +1 (650) 327-3270
Version	Amendment 5
Date	09 June 2022

Good Clinical Practice Statement

This study will be conducted in compliance with the protocol, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for Good Clinical Practice, 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

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APPROVAL STATEMENT

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

Signed and Dated:

[redacted]

PROTOCOL SYNOPSIS

Name of Sponsor	**Name of Active Ingredient**	**Study Number**
Corcept Therapeutics	Miricorilant	CORT118335-877

Title of Study

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

Study Centers

Approximately 35 sites in the US

Phase of Development

Phase 2

Study Objectives

Primary Efficacy

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

Secondary Efficacy

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

Exploratory

- To assess the efficacy of miricorilant versus placebo in reversing AIWG for each subgroup of patients taking:
  - Olanzapine
  - Risperidone or paliperidone (active risperidone metabolite)
  - Quetiapine
- To assess the efficacy of miricorilant versus placebo in reducing insulin resistance in patients not treated with insulin.
- To be assessed by patient group:
  - **In all patients**, change in adrenocorticotropic hormone (ACTH), serum cortisol, serum aldosterone, Brief Psychiatric Rating Scale (BPRS), Columbia Suicide Severity Rating Scale (C-SSRS), Clinical Global Impression (CGI) Scale, Obesity Weight Loss Quality of Life scale (OWLQOL), and Weight-Related Symptom Measure (WRSM).
  - **In patients with diabetes**, change in glycated hemoglobin (HbA1c) and fasting blood glucose.
  - **In patients with high blood pressure**, change in blood pressure.
- To evaluate the dose-response relationship between miricorilant and change in body weight.
- To evaluate the exposure-response relationship between miricorilant and change in body weight.

Safety

- To assess the safety of miricorilant versus placebo.

Pharmacokinetic (PK)

- To assess the PK of both dose levels of miricorilant.

Population

Obese patients (BMI ≥30 kg/m^2) with schizophrenia currently taking antipsychotic medication (olanzapine, risperidone, paliperidone, or quetiapine).

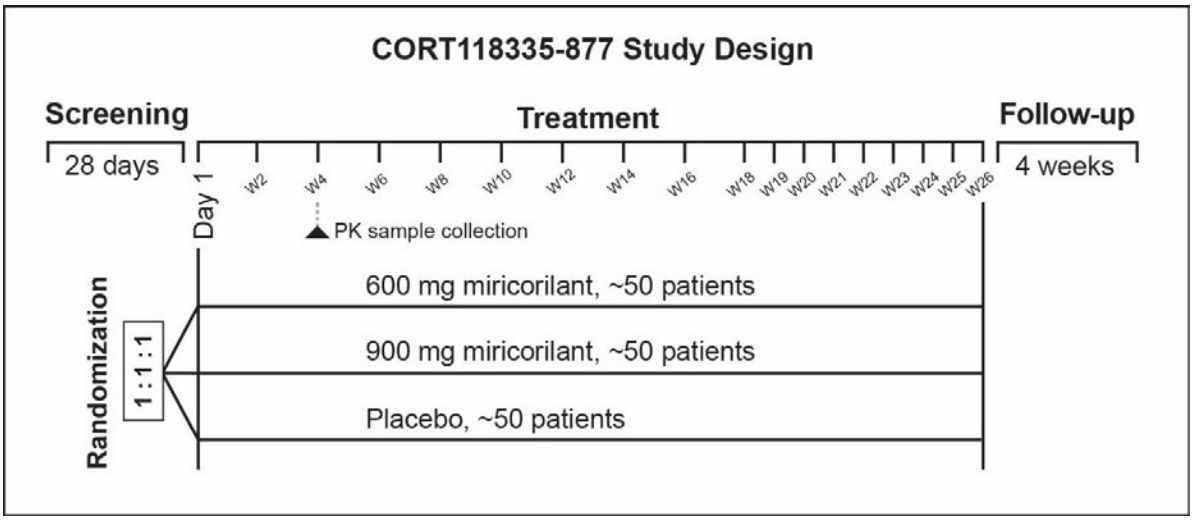
Number of Patients Planned

Approximately 150 patients will be enrolled in the study.

Methodology

This is a Phase 2, randomized, double-blind, placebo-controlled, multicenter study to evaluate the safety, efficacy, and PK of miricorilant in obese patients (BMI ≥30 kg/m^2) with schizophrenia currently taking olanzapine, risperidone, paliperidone, or quetiapine (Figure S1).

Figure S1 CORT118335-877 Study Design



Abbreviations: PK, pharmacokinetics; W, week.

Patients who are eligible for participation in the study will be randomized on Day 1 in a 1:1:1 ratio to 600 mg miricorilant, 900 mg miricorilant, or placebo, for 26 weeks of treatment. Randomization will be stratified by background antipsychotic medication (3 strata: olanzapine, risperidone or paliperidone, or quetiapine) to ensure approximately equal numbers of patients in each stratum are assigned to the 600 mg miricorilant, 900 mg miricorilant, and placebo groups.

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

Duration of Treatment and Duration of Study

The maximum expected duration of a patient's participation is 34 weeks consisting to the following study periods:

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

Key Inclusion Criteria

Please see Sections 4.1 and 4.2 for a complete list of all eligibility criteria.

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

- Are men or women ≥18 to ≤65 years old.
- Meet the criteria for schizophrenia based on medical history and the Mini International Neuropsychiatric Interview (MINI).
- Are currently taking olanzapine, risperidone, paliperidone, or quetiapine; long-acting, injectable formulations of olanzapine, risperidone, and paliperidone are acceptable.
- Have gained weight from treatment with olanzapine, risperidone, paliperidone, or quetiapine (patient must meet at least one criterion from each column):

Self-Assessment:	**Corroborated Reports:**
• Noticeable weight gain (~10 pounds or more) after initiation of antipsychotic medication	• Clinician or other health professional verifies that patient has gained weight (~10 pounds or more) since initiation of antipsychotic medication
• Increase in clothing size by two size units (e.g., size 10 to 14) after initiation of antipsychotic medication	• Caretaker or close friend/family member verifies that patient has gained weight (~10 pounds or more) since initiation of antipsychotic medication
• Increase in pant waist size by 4 inches (e.g., size 32 to 36) after initiation of antipsychotic medication	• Hospital or medical records indicate that patient has gained ≥5% of baseline weight since initiation of antipsychotic medication

- Have a BMI ≥30 kg/m^2.
- Have been on the same dose of antipsychotic medication for the last month prior to Screening.
- Are clinically stable and unlikely to require change to their antipsychotic medication (i.e., switch medication or change dose) through the duration of the study (34 weeks).
- Have a BPRS of ≤54 at Screening.

Key Exclusion Criteria

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

- Have one of the following psychiatric conditions:
  - 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 (C-SSRS-ideation) with the most recent episode occurring within the last 6 months.
    - Answer "Yes" to any of the 5 items (C-SSRS-behavior) with an episode occurring within the 6 months.
- Have participated in another Corcept study with miricorilant.
- Are currently taking more than one antipsychotic medication.
- Have a history of a medical condition affecting body weight (e.g., poorly controlled hyper- or hypothyroidism; eating disorder such as anorexia, bulimia, or binge eating; or polycystic ovary syndrome).

- Are currently using or plan to use 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 (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.
- 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 any elective surgery planned during the study.
- Have had liposuction within 1 year of Screening or have planned liposuction during the study.
- Have poorly controlled diabetes mellitus with 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 history of orthostatic hypotension with a systolic blood pressure decrease of ≥20 mm Hg or a diastolic blood pressure decrease of ≥10 mm Hg within the last year.
- Have a history of a seizure disorder.
- Are currently using any medications prohibited due to the potential for drug-drug interactions (DDI) with study treatments. Prohibited medications must be discontinued at least 5 half-lives prior to a patient receiving their first study treatment. Administration of concomitant medications are at the discretion of the Investigator and/or the Corcept Medical Monitor (see Section 5.5).
- Have a clinically significant electrolyte abnormality at Screening.
- Are currently using medication such as digoxin with an increased risk of toxicity in the event of electrolyte changes.
- Are taking an unstable dosage (change in the dose within 4 weeks of 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.

Study Drug, Dose, and Mode of Administration

Study Drug: Miricorilant tablet, 150 mg or placebo for miricorilant tablet, 150 mg.

Dose: 600 mg or 900 mg miricorilant, or placebo.

Patients will be instructed to take a total of 6 tablets at approximately the same time each day. Patients who participate in the PK substudy must take the study drug in the mornings; these patients will be instructed to take their dose in the clinic during the Week 4 visit.

- Those in the 600 miricorilant group will take 4 miricorilant tablets and 2 placebo tablets.

- Those in the 900 miricorilant group will take 6 miricorilant tablets.
- Those in the placebo group will take 6 placebo tablets.

Mode of Administration: oral administration with 8 oz (240 mL) of water, along with food.

Criteria for Evaluation

Study endpoints corresponding to study objectives are listed below.

Primary Efficacy Endpoint

Change from Baseline to Week 26 in body weight for both dose levels of miricorilant versus placebo.

Secondary Efficacy Endpoints

The following endpoints will be assessed:

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

Exploratory Endpoints

The following endpoints will be assessed relative to Baseline:

- Change in body weight for miricorilant versus placebo in each subgroup of patients taking:
  - Olanzapine
  - Risperidone or paliperidone
  - Quetiapine
- Change in Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) in patients who are not treated with insulin.

<u>In all patients:</u>

- Changes in ACTH, serum cortisol, and serum aldosterone (pharmacodynamic assessments).
- Changes in BPRS, C-SSRS, CGI, OWLQOL, and WRSM.

<u>In patients with diabetes:</u>

- Change in HbA1c.
- Change in fasting blood glucose.

<u>In patients with high blood pressure:</u>

- Change in blood pressure.

Safety Endpoints

The following endpoints will be assessed for miricorilant versus placebo:

- Incidence of TEAEs, AEs, and SAEs.
- Changes from Baseline in clinical laboratory tests (hematology and chemistry panels).
- Changes from Baseline in physical examinations and vital sign.
- Changes from Baseline in ECG parameters.

Pharmacokinetic Endpoints

- Key PK parameters estimated from steady-state plasma concentration.

Statistical Methods

Statistical Analyses

Analysis of the Primary Efficacy Endpoints

The primary efficacy endpoint is based on the change in body weight from Baseline to Week 26. The primary analysis will use a mixed-effect model with repeated measures (MMRM) with change in body weight at each visit as the outcome variable; baseline body weight as a covariate; and antipsychotic medication (stratification factor), randomized treatment (600 mg or 900 mg miricorilant or placebo), visit, and treatment-by-visit interaction as fixed effects.

The difference in body weight change at Week 26 between each miricorilant treatment group and placebo will be estimated from the model along with its associated 95% confidence interval (CI).

The primary efficacy analysis will use the Efficacy Evaluable population. Neither CIs nor p-values will be adjusted for multiplicity.

Analysis of the Secondary Efficacy Endpoints

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

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 as a covariate, and antipsychotic medication and randomized treatment as fixed effects, will be used to compare each miricorilant dose group to placebo.

Waist-to-hip ratio will be analyzed using similar models as the primary analysis of weight change. Differences between each miricorilant dose group and placebo will be estimated along with corresponding 95% CIs. Waist-to-hip ratio data may require a log-transformation prior to analysis.

Analyses of Exploratory Endpoints

The relationship between background antipsychotic medication and efficacy will be explored through subgroup analyses. Specifically, 3 MMRM analyses will be performed, one for each subgroup of patients taking olanzapine, risperidone or paliperidone, or quetiapine. Each MMRM will be similar to the primary analysis except all miricorilant dose groups will be combined into a single treatment group. Each model will use change in body weight at each visit as the outcome variable; baseline body weight as a covariate; and treatment (miricorilant or placebo), visit, and treatment-by-visit interaction as fixed effects. For each background medication, the difference in body weight change at Week 26 between the combined miricorilant dose groups and placebo will be estimated from the appropriate model along with its associated 95% CI and p-value.

Analyses of continuous endpoints assessed at multiple post-treatment timepoints, such as the change in BPRS, CGI, OWLQOL, and WRSM from Baseline to Week 26 will be analyzed using models similar to the primary analysis of body weight change. C-SSRS results will be summarized descriptively. Endpoints like ACTH, serum cortisol, and serum aldosterone that are measured only at Baseline and Week 26 will be assessed using analysis of covariance (ANCOVA) models that include the change in the endpoint between Baseline and Week 26 as the outcome variable, baseline body weight as a covariate, and antipsychotic medication and randomized treatment as factors. 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.

HOMA-IR will be analyzed using similar models as the primary analysis of weight change. Differences between each miricorilant dose group and placebo will be estimated along with corresponding 95% CIs. HOMA-IR data may require a log-transformation prior to analysis.

Dose response will be evaluated using an MMRM identical to that used for the primary analysis except that the placebo group will not be included. The difference between the miricorilant dose groups in the change in body weight at Week 26 will be estimated from the model using a linear contrast. The difference will be accompanied by an associated 95% CI and p-value.

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.

Pharmacokinetic Analysis

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.

Details of the PK analyses will be described in a PK analysis plan finalized before database lock.

Sample Size

The planned sample size is 150 subjects randomized 1:1:1 across 2 miricorilant treatment groups and 1 placebo group.

Fifty patients per group will ensure at least 90% power to detect a difference of 5 kg in mean change from Baseline in body weight between placebo and either miricorilant treatment group. These calculations assume a common standard deviation of 6 kg and a 0.05 two-sided significance level two-sample z-test. A drop-out rate of 40% from Baseline to Week 26 is assumed in this calculation.

Randomization will be stratified by the type of antipsychotic medication used (one stratification factor with 3 levels). If ≥20 patients complete 26 weeks of treatment (10 patients treated with miricorilant and 10 patients treated with placebo) in one of the allowed antipsychotic medication groups (olanzapine, risperidone or paliperidone, or quetiapine), this sample size provides 60% power to detect a difference in body weight change of 5 kg between the miricorilant and placebo groups, at alpha=0.1 level for that antipsychotic medication. The sample size estimates have not been adjusted for multiple comparisons.

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List of Abbreviations and Definitions

Abbreviation	Definition
ACTH	adrenocorticotropic hormone
AE	adverse event
AIWG	antipsychotic-induced weight gain
ALT	alanine aminotransferase
AR	androgen receptor
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BMI	body mass index
BPRS	Brief Psychiatric Rating Scale
CDC	Centers for Disease Control and Prevention
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
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
HME	hot melt extrudate
HOMA-IR	Homeostatic model assessment of insulin resistance
IB	Investigator's Brochure

Abbreviation	Definition
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IRB	Institutional Review Board
ITT	Intent-to-Treat
IWRS	interactive web response system
K_i	inhibition constant
MINI	Mini International Neuropsychiatric Interview
MMRM	mixed-effect model with repeated measures
MR	mineralocorticoid receptor
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
OWLQOL	Obesity Weight Loss Quality of Life
PK	pharmacokinetic(s)
PR	progesterone receptor
QTc	corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's equation: $QTcF=QT/(RR^{1/3})$
RSI	Reference Safety Information
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
WBC	white blood cell
WRSM	Weight-Related Symptom Measure

1 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 Therapeutic Area

Antipsychotic-induced weight gain (AIWG) is a condition in which patients with schizophrenia and other disorders treated with antipsychotic medications gain weight, leading to increases in diabetes mellitus, dyslipidemia, cardiovascular disease, and mortality.

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).

1.1.1 Background

Atypical antipsychotic medications were initially developed to overcome extrapyramidal effects (e.g., tardive dyskinesia) associated with first-generation antipsychotic medications. Atypical antipsychotic medications, although efficacious, tend to cause significantly more weight gain in patients than first-generation medications. Among the commonly used atypical antipsychotic medications, clozapine and olanzapine, followed by risperidone and quetiapine appear to cause the most weight gain (ADA/APA/AACE/NAASO 2004). In one study, olanzapine and clozapine caused between 4.0 to 4.5 kg of weight gain on a standard dose over the course of 10 weeks (Allison and Casey 2001). In addition to weight gain, patients on atypical antipsychotic medications develop drug-induced metabolic changes including increased insulin resistance and elevated levels of cholesterol and serum triglycerides that significantly increase their risk for cardiovascular disease (Dayabandara et al. 2017). Consequently, patients with schizophrenia have a 2–3 fold increased risk of mortality compared with the general population, corresponding to a 10–25 year reduction in life expectancy (Laursen et al. 2012). Furthermore, weight gain is also associated with discontinuation of antipsychotic medications, leading to a decrease in their effectiveness (Liebermann et al. 2005).

1.1.2 Therapeutic Hypothesis

The mechanism of AIWG remains poorly understood. Antipsychotic medications act on 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 also been implicated with the use of atypical antipsychotics. For example, rats treated with clozapine showed an increase in corticosterone (Tulipano et al. 2007).

In humans, there is evidence for a role for the glucocorticoid receptor (GR) in AIWG. In healthy volunteers treated with either olanzapine or risperidone, mifepristone, a GR antagonist, ameliorated the weight gain from the antipsychotic medication (Gross et al. 2009, Gross et al. 2010).

More recently, miricorilant, which is a mixed agonist/antagonist of the GR and an antagonist of the mineralocorticoid receptor (MR), has been shown to mitigate weight gain in healthy volunteers taking olanzapine (Study CORT118335-852).

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

Miricorilant, a mixed agonist/antagonist of the GR and an antagonist of the MR, is currently being developed for the treatment of AIWG. The goals of this study (CORT118335-877) are to evaluate the safety, efficacy, and pharmacokinetics (PK) of miricorilant in reversing AIWG in obese patients (body mass index [BMI] ≥30 kg/m^2) with schizophrenia currently taking olanzapine, risperidone, paliperidone (active metabolite of risperidone), or quetiapine.

Further information about miricorilant is provided in the Investigator's Brochure (IB).

1.2.1 Nonclinical Summary

1.2.1.1 Pharmacology

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

1.2.1.1.1 In Vitro Pharmacology

Miricorilant binds competitively and reversibly to the GR with high affinity (1.2 nM). Functional GR antagonism has been demonstrated in vitro by the ability of miricorilant to block the effects of dexamethasone (a potent and selective GR agonist) on tyrosine aminotransferase (TAT) activity in a human liver carcinoma cell line (inhibition constant [K_i], 100 nM) and a rat hepatoma cell line (K_i, 11 nM). Miricorilant prevented the dexamethasone-induced increase in TAT activity in primary hepatocytes from mice, monkeys, and humans. Miricorilant is also an antagonist of the MR, and has shown activity in both a reporter gene assay (K_i, 148 nM) and a protein:protein interaction assay (K_i, 140 nM). Both GR and MR antagonism are considered to contribute to the in vivo pharmacological activity of miricorilant.

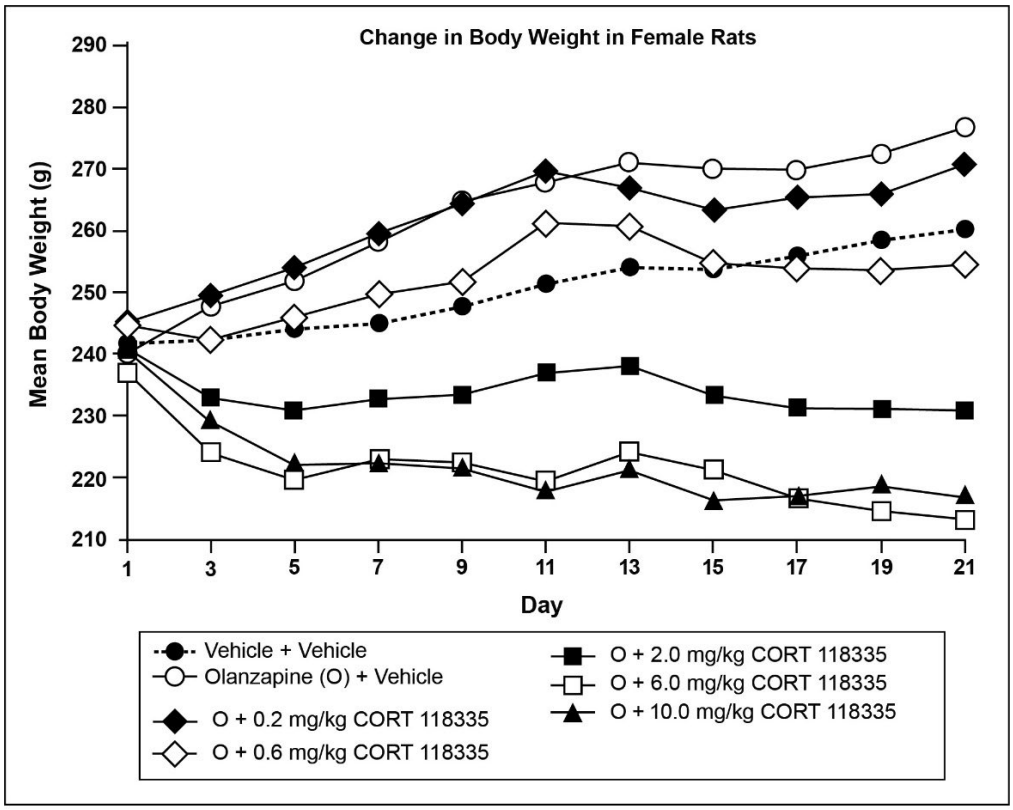
1.2.1.1.2 In Vivo Pharmacology

The most commonly used animal model of AIWG 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 et al. 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.

Three studies (MPI 950-033, MPI 950-034, and MPI 950-035) evaluated the ability of miricorilant, at various doses, to prevent weight gain in female rats (10 per group) that were administered the antipsychotic medication olanzapine and fed a normal diet. 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).

In Study MPI 950-035, miricorilant doses ≥0.6 mg/kg/day demonstrated a dose-dependent inhibition of olanzapine-induced weight gain (Figure 1; Hunt et al. 2012).

Figure 1 Effect of Miricorilant on Body Weight in Female Rats Given Olanzapine



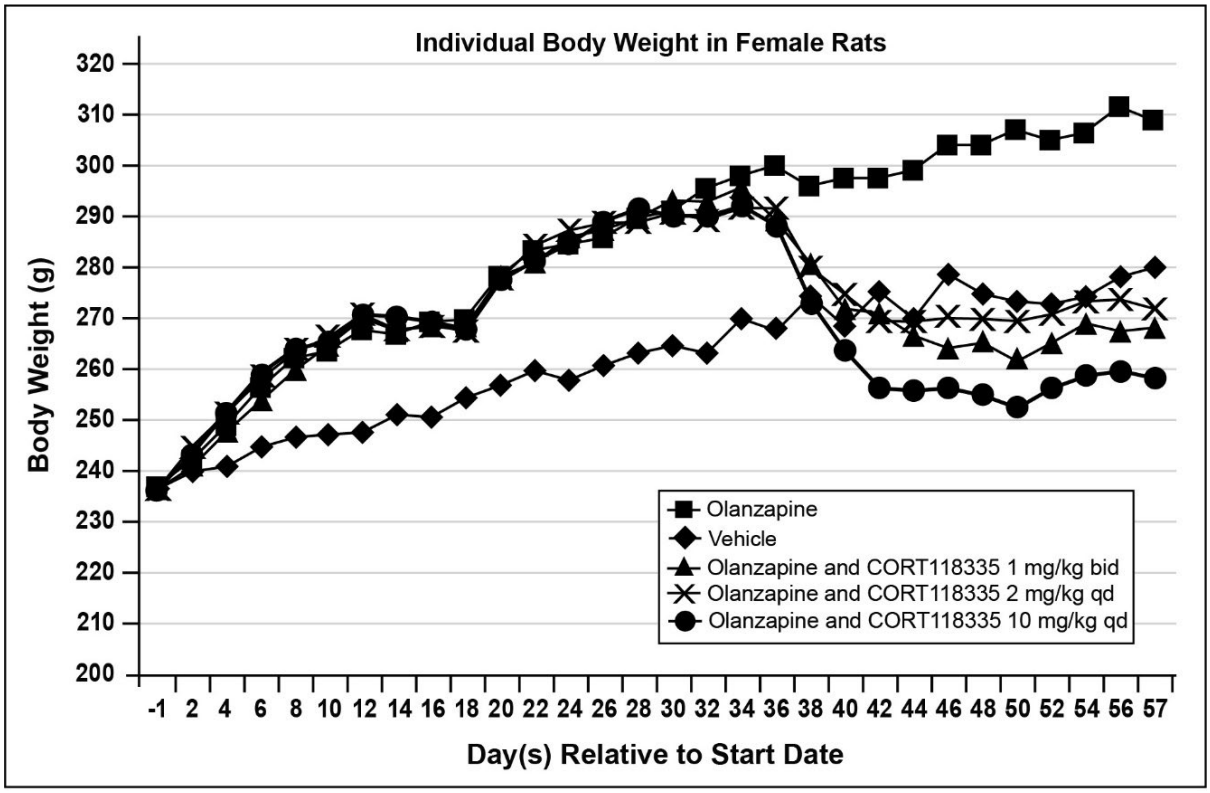
Source: Hunt et al. 2012, MPI 950-035.
CORT118335=miricorilant.
Abbreviation: O, olanzapine.

The ability of miricorilant to reverse (rather than prevent) olanzapine-induced weight gain in female rats was investigated in 3 separate studies (MPI 950-144, RenaSci RS1738, and RenaSci RS1854).

In the first study (MPI 950-144), rats were fed a normal diet, and were either administered olanzapine at a dose of 1.2 mg/kg twice a day, (i.e., 2.4 mg/kg/day, for 56 consecutive days) or received only vehicle throughout the duration of the study.

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 olanzapine-induced increase in body weight 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 or a split dose of 1 mg/kg twice a day, were similar. Effects were observed from the first week of dosing and persisted through the remainder of the study.

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



Source: MPI 950-144.
CORT118335=miricorilant.
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 resulted 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 was investigated in two studies (RenaSci RS1738 and RS1854), and doses as low as 0.5 mg/kg/day fully reversed the effects of olanzapine.

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). Additionally, in vitro data showed the potential for modest inhibition of CYP3A4, CYP2C8, and CYP2C9 by miricorilant (Corcept PK-118335-004 and Corcept PK-118335-009).

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 was evaluated in preliminary ascending single- and repeat-dose studies followed by Good Laboratory Practice (GLP) 28-day, 91-day repeat-dose and chronic toxicology studies in mice and monkeys. Definitive GLP reproductive toxicology studies were conducted in mice and rabbits, and 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), were performed. 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 a maximum inhibition of hERG-mediated potassium currents of 23.8%.

Mouse and monkey GLP 28 day (1 month), 91 day (3-month), 179 day (6-month; mice) and 270 day (9-month; monkey) general toxicology studies were conducted with miricorilant, which was dosed daily by oral gavage:

- Mice were administered doses of 30, 100, 300, or 500 mg/kg for 28 days (MPI 950-126) and 30, 100, or 500 mg/kg for 91 days (MPI 950-140). No adverse effects were observed at any dose in either of these two studies. Therefore, the no-observed-adverse-effect-level (NOAEL) was 500 mg/kg.
- Monkeys administered doses of 20, 100, or 400 mg/kg for 28 days showed no adverse effects at any dose in this study. Therefore, the NOAEL was 400 mg/kg (MPI 950-127). Monkeys were administered doses of 20, 50, or 200 mg/kg for 91 days. Although no adverse effects were noted in female monkeys (for a NOAEL of 200 mg/kg), the NOAEL was 50 mg/kg for male monkeys, because adverse clinical effects, specifically abnormal feces, decreased activity, lack of appetite, hunched posture, dehydration and ataxia, were noted at the highest dose (MPI 950-139).
- Mice were administered doses of 30, 100 and 300 mg/kg for 6 months. No adverse effects were observed, and the NOAEL was 300 mg/kg in both sexes (MPI 950-155).
- Monkeys were administered doses of 15, 50 and 150 mg/kg for 9 months. No adverse effects were observed, and the NOAEL was 150 mg/kg in both sexes (MPI 950-156).

Other treatment-related findings in the nonclinical studies are considered related to the mode of action of miricorilant as a GR mixed agonist/antagonist 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 definitive GLP reproductive toxicology study conducted in pregnant mice, miricorilant was administered daily by oral gavage at doses of 1, 10 and 100 mg/kg/day (MPI 950-177) from gestation day (GD) 6 through 15. The NOAEL for maternal toxicity was 10 mg/kg/day due to reduced body weight gain at the 100 mg/kg/day dose. The NOAEL for developmental toxicity was 1 mg/kg/day. At higher doses skeletal malformations were observed, including cleft palate.
- In the definitive GLP reproductive toxicology study conducted in female rabbits (MPI 950-178), miricorilant was administered daily by oral gavage at doses of 1, 3, and 10 mg/kg/day from GD 7 through 19. The NOAEL for maternal toxicity was 10 mg/kg/day and the NOAEL for developmental toxicity was 1 mg/kg/day. A dose of 10 mg/kg/day resulted in adverse pregnancy outcomes (abortions, resorbed fetuses, postimplantation loss), decreased gravid uterine weights and decreased fetal body weight. Skeletal abnormalities were also observed at this dose, although these were considered non-adverse. A dose of 3 mg/kg/day resulted in decreased uterine weights and decreased fetal weights.

These data indicate that 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 and men with partners of childbearing potential in clinical studies must use highly efficacious forms of birth control as outlined in Section 4.6.4.

Additional 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 ongoing Study CORT118335-853) and one Phase 2 study (Study CORT118335-876; GRATITUDE). Study CORT118335-876 is an ongoing Phase 2, double-blind study conducted in obese patients with schizophrenia to assess the ability of miricorilant in reversing recent AIWG. Available safety and PK data from these five 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 in suspension. 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 as single doses under both 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 subject experienced a serious adverse event (SAE) of 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

Holter monitoring was conducted in the MAD/suspension parts of the study. No subject had an increase in QTcF >30 ms based on Holter readings.

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 21–23 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 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 tablets) 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 exposure 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 miricorilant tablets) is approximately 25% lower than the predicted C_{max} of 140 ng/mL based on dose-proportionality.

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

1.3.2 Phase 1 Study CORT118335-851

CORT118335-851 was an open-label study conducted with [^{14}C]-miricorilant to assess the absolute oral 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 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

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. No SAEs or AEs leading to discontinuation were reported.

No clinically significant findings in any of the vital signs or laboratory evaluations were reported. Single ECGs were obtained unless abnormalities were detected. No subject recorded QTcF intervals that were >450 msec at any time point and no subject had increases in QTcF interval from baseline that were >30 msec.

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%) $AUC_{0\text{-}24}$, 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 this Phase 2 study (CORT118335-877).

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.

1.3.5 Phase 2 Study CORT118335-876 (GRATITUDE)

This is a Phase 2, randomized, double-blind, placebo-controlled study to investigate the ability of miricorilant to treat recent AIWG caused by any oral or injectable atypical antipsychotic medication (except clozapine) in obese patients (BMI ≥30 kg/m^2) with schizophrenia or bipolar disorder; patients who have been on antipsychotic medication for 18 months or less and have demonstrated weight gain of ≥5% within 6 months of starting the medication are eligible. In this multi-center study, approximately 70 patients with schizophrenia or bipolar disorder, and AIWG will be randomized in a 1:1 ratio to 600-mg miricorilant (6 × 100 mg tablets) or placebo for 12 weeks, and the safety, efficacy, and PK of miricorilant will be evaluated.

This study is currently ongoing.

Safety Results

As of June 25, 2020, no deaths have been reported in this ongoing double-blinded study.

One patient presented with SAEs of malignant hyperthermia and sympathomimetic drug intoxication following worsening schizophrenia after self-discontinuation of his antipsychotic medication. This event was considered not related to study drug (miricorilant or placebo).

1.4 Rationale for Study Design and Dosage Regimen

1.4.1 Design Considerations

This is a study of miricorilant, a mixed agonist/antagonist of the GR and an antagonist of the MR, in obese patients with schizophrenia taking antipsychotic medications. There is evidence that GR antagonism may alleviate AIWG. In healthy volunteers treated with olanzapine or risperidone, mifepristone (a GR antagonist) ameliorated weight gain associated with these medications (Gross et al. 2009, Gross et al. 2010). Additionally, results from the Phase 1 Study CORT118335-852 show that miricorilant has been shown to mitigate weight gain in healthy volunteers taking olanzapine.

The ongoing Phase 2 Study CORT118335-876 (GRATITUDE) is designed to investigate the ability of miricorilant to treat recent AIWG in patients with schizophrenia or bipolar disorder on antipsychotic medication when treated for 12 weeks. In this study, patients with schizophrenia with long-standing weight gain due to antipsychotic medication will be treated for a longer duration (26-week regimen) with miricorilant to evaluate its ability to reverse AIWG.

Specifically, this study will compare 2 doses of miricorilant (600 mg and 900 mg) to placebo, and determine whether once daily dosing of miricorilant for 26 weeks results in reversal of AIWG in obese patients (BMI ≥30 kg/m^2) with schizophrenia who have been taking olanzapine,

risperidone, paliperidone, or quetiapine. This study will be conducted in the US at approximately 35 sites and will randomize approximately 150 obese patients to a 1:1:1 ratio of 600 mg miricorilant, 900 mg miricorilant, or placebo in a double-blind manner to reduce bias.

The study will consist of 4 weeks of Screening, 26 weeks of Treatment, and 4 weeks of Follow-up. The efficacy of miricorilant versus placebo in reversing AIWG will be assessed. Clinical benefit will also be assessed through patient-reported outcomes such as the Obesity Weight Loss Quality of Life scale (OWLQOL) and Weight-Related Symptom Measure (WRSM) questionnaires. Routine assessments of safety will consist of AE monitoring, measurement of vital signs, 12-lead ECG recordings, physical examination, and clinical laboratory safety tests. In the PK substudy, to be conducted in a subgroup of approximately 45 patients, samples will be collected to determine standard PK parameters for miricorilant.

1.4.2 Rationale for Dose Selection and Regimen

Miricorilant is effective at mitigating and reversing weight gain in rat studies described in Section 1.2.1. 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; likewise miricorilant at 900 mg as a divided dose for 14 days confirmed these weight mitigation results (CORT118335-852, summarized in Section 1.3.3). Study CORT118335-877 is designed to evaluate the safety and tolerability of miricorilant in reversing long-standing AIWG with the same total doses used in Study CORT118335-852. The 600 mg dose is predicted to be a minimally effective dose. The 900 mg dose given once daily is included as a second dose in this study to evaluate the efficacy and the dose/exposure relationship. The safety of 900 mg has been previously established in Phase 1 Studies CORT118335-850 and CORT118335-852.

1.5 Benefits and Risks

Miricorilant has shown efficacy in rat models of AIWG and has also been shown to mitigate weight gain in healthy volunteers taking olanzapine. 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 on atypical antipsychotic medications develop drug-induced metabolic changes that significantly increase their risk for cardiovascular disease (Dayabandara et al. 2017). Consequently, patients with schizophrenia have a 2–3 fold increased risk of mortality compared with the general population, corresponding to a 10–25 year reduction in life expectancy (Laursen et al. 2012). Reversal or possibly prevention of AIWG is expected to provide a clinically meaningful improvement in general health outcomes and life expectancy in patients taking antipsychotic medications.

Based on the totality of data for miricorilant, the potential for clinically relevant drug-drug interactions in this study is low. The elimination of olanzapine, risperidone, paliperidone, and quetiapine is primarily through hepatic metabolism with contribution by CYP1A2, CYP2D6, and/or CYP3A4. Although miricorilant has shown modest inhibitory potential of CYP3A4 in vitro (Corcept PK-118335-004), miricorilant can be used in combination with these antipsychotic medications. Additionally, there is no evidence that GR antagonism interferes with the efficacy of these antipsychotic medications.

The risk of clinically significant safety concerns is considered low. However potential adverse effects of miricorilant may include a combination of 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 MR antagonism (e.g., hyperkalemia and hypotension).

Olanzapine, risperidone, paliperidone, and quetiapine additionally have both orthostatic hypotension and drug induced leukopenia/neutropenia as reported adverse reactions. Patients who are at risk for clinically significant leukopenia/neutropenia or clinically significant orthostatic hypotension will be excluded from the study. Orthostatic vital signs will be measured at each study visit, including follow-up.

Patients will be closely monitored during the study. Standard safety tests such as chemistry panels (refer to Table 4) will be performed at scheduled visits 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 or oral hydrocortisone and intravenous fluids. Further information for monitoring and treating excessive GR or MR antagonism is provided in Section 5.3.2 and 5.4.3.

2 STUDY OBJECTIVES

2.1 Primary Efficacy Objective

- To assess the efficacy of both dose levels of miricorilant versus placebo in reversing AIWG.

2.2 Secondary Efficacy Objectives

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

2.3 Exploratory Objectives

- To assess the efficacy of miricorilant versus placebo in reversing AIWG for each subgroup of patients taking:
  - Olanzapine
  - Risperidone or paliperidone (active risperidone metabolite)
  - Quetiapine
- To assess the efficacy of miricorilant versus placebo in reducing insulin resistance in patients not treated with insulin.
- To be assessed by patient group:
  - **In all patients**, change in adrenocorticotropic hormone (ACTH), serum cortisol, serum aldosterone, Brief Psychiatric Rating Scale (BPRS), Columbia Suicide Severity Rating Scale (C-SSRS), Clinical Global Impression (CGI) Scale, Obesity Weight Loss Quality of Life scale (OWLQOL) and Weight-Related Symptom Measure (WRSM).
  - **In patients with diabetes**, change in glycated hemoglobin (HbA1c) and fasting blood glucose.
  - **In patients with high blood pressure**, change in blood pressure.
- To evaluate the dose-response relationship between miricorilant and change in body weight.
- To evaluate the exposure-response relationship between miricorilant and change in body weight.

2.4 Safety Objectives

- To assess the safety of miricorilant versus placebo.

2.5 Pharmacokinetics Objective

- To assess the PK of both dose levels of miricorilant.

3 STUDY DESIGN

3.1 Overall Design

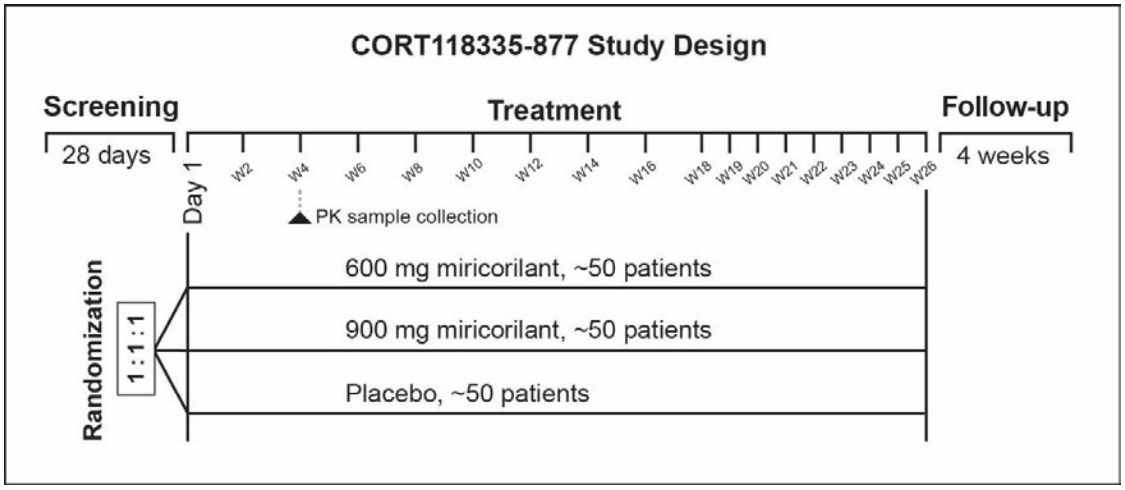
This is a Phase 2, randomized, double-blind, placebo-controlled, multicenter study to evaluate the safety, efficacy, and PK of miricorilant in obese patients (BMI ≥30 kg/m^2) with schizophrenia currently taking olanzapine, risperidone, paliperidone, or quetiapine.

The study consists of the following study periods:

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

The study design is illustrated in Figure 3.

Figure 3 CORT118335-877 Study Design



Abbreviations: PK, pharmacokinetics; W, week.

Approximately 150 patients who are eligible for participation in the study will be randomized on Day 1 in a 1:1:1 ratio to 600 mg miricorilant, 900 mg miricorilant, or placebo, for 26 weeks of treatment. Randomization will be stratified by background antipsychotic medication (3 strata: olanzapine, risperidone or paliperidone, or quetiapine) to ensure approximately equal numbers of patients within each stratum are assigned to the 600 mg miricorilant, 900 mg miricorilant, and placebo groups. See Section 9.4 for details regarding sample size calculation.

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

3.2 Study Endpoints

3.2.1 Primary Efficacy Endpoint

Change from Baseline to Week 26 in body weight for both dose levels of miricorilant versus placebo.

3.2.2 Secondary Efficacy Endpoints

The following endpoints will be assessed:

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

3.2.3 Exploratory Endpoints

The following endpoints will be assessed relative to Baseline:

- Change in body weight for miricorilant versus placebo in each subgroup of patients taking:
  - Olanzapine
  - Risperidone or paliperidone
  - Quetiapine
- Change in Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) in patients who are not treated with insulin.

In all patients:

- Changes in ACTH, serum cortisol, and serum aldosterone (pharmacodynamic assessments).
- Changes in BPRS, C-SSRS, CGI, OWLQOL, and WRSM.

In patients with diabetes:

- Change in HbA1c.
- Change in fasting blood glucose.

In patients with high blood pressure:

- Change in blood pressure.

3.2.4 Safety Endpoints

The following endpoints will be assessed for miricorilant versus placebo:

- Incidence of TEAEs, AEs, and SAEs.
- Changes from Baseline in clinical laboratory tests (hematology and chemistry panels).
- Changes from Baseline in physical examinations and vital sign measurements.
- Changes from Baseline in ECG parameters.

3.2.5 Pharmacokinetic Endpoints

Key PK parameters will be estimated from steady state plasma concentrations of miricorilant (see Section 6.6, Table 5 for PK variables to be analyzed).

3.3 Number of Patients and Study Participation

3.3.1 Number of Patients

Approximately 150 patients will be randomized on Day 1 in a 1:1:1 ratio to 600 mg miricorilant, 900 mg miricorilant, or placebo, for 26 weeks of treatment. The PK substudy will be conducted at the Week 4 visit; approximately 45 patients are expected to participate.

3.3.2 Duration of Patient Participation

The maximum expected duration of a patient's participation is 34 weeks (4 weeks of Screening, 26 weeks of Treatment, and 4 weeks of Follow-up).

3.4 Definitions: Enrollment, Study Completer, End of Treatment, and End of Study

3.4.1 Enrollment

Patients are considered enrolled in the study when they meet the study enrollment criteria.

3.4.2 Study Completer

Patients are considered to have completed the study if they complete all 26 weeks of Treatment.

3.4.3 End of Treatment

The end of treatment is defined as the date on which the patient received his or her last dose of the study drug, which may be the end of the Treatment Period if the patient received all doses of the study drug or may be earlier, if the patient discontinued the study drug before the designated stopping point at Week 26.

3.4.4 End of Study

The end of study is defined as the date of last contact (i.e., visit, telephone, e-mail) with the last patient in the study.

3.5 Study Termination by Sponsor

If Corcept (the Sponsor), the 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 the Sponsor 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 the patients enrolled in the study.

- Decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product.

Study termination (if required) and follow-up will be performed in compliance with applicable regulations and guidelines.

4 STUDY POPULATION

The following eligibility criteria are designed to select obese patients (BMI ≥30 kg/m^2) with schizophrenia currently taking olanzapine, risperidone, paliperidone, or quetiapine, 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. Meet the criteria for schizophrenia based on medical history and the Mini International Neuropsychiatric Interview (MINI).
4. Are currently taking olanzapine, risperidone, paliperidone, or quetiapine; long-acting, injectable formulations of olanzapine, risperidone, paliperidone are acceptable.
5. Have gained weight from treatment with olanzapine, risperidone, paliperidone, or quetiapine (patient must meet at least one criterion from each column):

Self-Assessment:	**Corroborated Reports:**
• Noticeable weight gain (~10 pounds or more) after initiation of antipsychotic medication	• Clinician or other health professional verifies that patient has gained weight (~10 pounds or more) since initiation of antipsychotic medication
• Increase in clothing size by two size units (e.g., size 10 to 14) after initiation of antipsychotic medication	• Caretaker or close friend/family member verifies that patient has gained weight (~10 pounds or more) since initiation of antipsychotic medication
• Increase in pant waist size by 4 inches (e.g., size 32 to 36) after initiation of antipsychotic medication	• Hospital or medical records indicate that patient has gained ≥5% of baseline weight since initiation of antipsychotic medication

6. Have a BMI ≥30 kg/m^2.
7. Have been on the same dose of antipsychotic medication for the last month prior to Screening.
8. Are clinically stable and unlikely to require change to their antipsychotic medication (i.e., switch medication or change dose) through the duration of the study (34 weeks).
9. Have a BPRS of ≤54 at Screening.
10. Agree to use highly effective methods of contraception throughout the study and for at least 28 days after the last dose of assigned treatment (for women of childbearing potential or men with a sexual partner of childbearing potential); see Section 4.6.4 and 4.6.5.

4.2 Exclusion Criteria

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

1. Have one of the following psychiatric conditions:
    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.
        ii. Answer "Yes" to any of the 5 items (C-SSRS-behavior) with an episode occurring within the 6 months.
2. Have participated in another Corcept study with miricorilant.
3. Are currently taking more than one antipsychotic medication.
4. Have a history of a medical condition affecting body weight (e.g., poorly controlled hyper- or hypothyroidism; eating disorder such as anorexia, bulimia, or binge eating; or polycystic ovary syndrome).
5. 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.
6. 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.
7. Have any elective surgery planned during the study.
8. Have had liposuction within 1 year of Screening or have planned liposuction during the study.
9. Have poorly controlled diabetes mellitus with HbA1c >10% or a fasting blood glucose >200 mg/dL.
10. 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.

11. Have a history of symptomatic hypotension with a systolic blood pressure <100 mm Hg or a diastolic blood pressure <60 mm Hg.
12. Have a history of orthostatic hypotension with a systolic blood pressure decrease of ≥20 mm Hg or a diastolic blood pressure decrease of ≥10 mm Hg within the last year.
13. Have a history of a seizure disorder.
14. Are currently using any medications prohibited due to the potential for drug-drug interactions (DDI) with the study drug. Prohibited medications must be discontinued at least 5 half-lives prior to a patient receiving their first dose of the study drug. Administration of concomitant medications are at the discretion of the Investigator and/or the Corcept Medical Monitor (see Section 5.5).
15. Have a clinically significant electrolyte abnormality at Screening.
16. Are currently using medication such as digoxin with an increased risk of toxicity in the event of electrolyte changes.
17. Are taking an unstable dosage (change in the dose within 4 weeks of Screening) of a medication that may change the fluid or electrolyte status such as a diuretic
18. 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/1.73 m^2.
    d. AST or ALT >3 × the upper limit of normal.
    e. White blood cell (WBC) count below the limit of normal.
    f. Absolute neutrophil count <1,500 neutrophils/µL.
19. Have a clinically significant ECG abnormality as judged by the Investigator.
20. Have a QTcF >450 ms for men or QTcF >470 ms for women.
21. Are breast feeding, pregnant, or planning a pregnancy.
22. Have any clinical condition or significant concurrent disease judged by the Investigator to complicate the evaluation of the study drug.
23. Previous exposure to investigational drugs taken within 3 months or 5 half-lives of the investigational drug prior to Screening, whichever is longer.
24. Are employees or immediate family members of the clinical site staff or Corcept employees.
25. 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).
26. Have a history of illicit drug use within the last 12 months including, but not limited to, cocaine, heroin, ecstasy, lysergic acid diethylamide (LSD) or other hallucinogens, and ketamine.
27. Are seropositive for hepatitis B or hepatitis C.
28. Patients with a known HIV infection.
29. 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 did not meet eligibility criteria for the study and were not randomized to the study drug.

Patients who have an exclusionary laboratory, ECG, or vital sign result on initial screening tests may have that assessment repeated in consultation with the Corcept Medical Monitor 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 with the approval of the Corcept 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 the study drug 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 administration of the study drug, 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 of Study Drug

Study drug 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 but are not limited to 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 26 (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 26 visit at the very least in addition to the ET and Follow-Up visits. The date when the patient discontinues the study drug and the reason for discontinuation must be recorded on the eCRF.

For guidelines about temporary interruption of study drug, see Section 5.4.

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 drug and/or failure to adhere to the study requirements, as specified in protocol.
- Lost to follow-up (before a patient is determined to be lost to follow-up, reasonable efforts will be made to contact the patient and complete study termination procedures).
- 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. As noted above, if a patient wishes to withdraw consent to further participation in the study entirely, including follow-up, this should be clearly documented (1) in the patient's medical record and signed by the Investigator and (2) in the clinical study database (eCRF).

4.5 Replacement of Patients

Not applicable.

4.6 Restrictions/Requirements/Recommendations During Study

The following apply to patients in this study (prohibited or limited-use medications are described in Section 5.5).

4.6.1 Dietary Restrictions

Patients will be asked to follow a healthy diet according to the American Heart Association guidelines (AHA 2020).

4.6.2 Alcohol

Patients will be advised to limit alcohol use (also see Section 4.2 regarding alcohol abuse).

4.6.3 Activity

Patients should engage in physical activity as possible and are recommended to follow the Centers for Disease Control and Prevention (CDC) guidelines of 150 minutes per week of moderate-intensity aerobic activity (CDC 2020). Patients are advised to gradually increase their activity level to meet this guideline.

4.6.4 Childbearing Potential and Contraception

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

All female patients of childbearing potential (including all women <50 years old, women whose surgical sterilization was performed <6 months prior to Screening, and women who have had a menstrual period in the last 12 months) will take pregnancy tests at scheduled visits (Appendix A). The Screening pregnancy test will be a blood test. All subsequent pregnancy tests will be urine tests.

- A female patient is of childbearing potential if, in the opinion of the Investigator, she is biologically capable of having children.
- Female patients who are considered not of childbearing potential must meet at least 1 of the two following criteria:
  a. Have undergone a documented hysterectomy and/or bilateral oophorectomy.
  b. 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.

Female patients of childbearing potential are required and must agree to use a highly effective method of contraception throughout the study and for at least 28 days following the last dose of study drug administration.

Male patients with female partners are required and must agree to use 2 forms of contraception, one of which is a barrier method, throughout the study and for at least 28 days following the last dose of study drug administration.

Highly effective forms of contraception include:

a. Abstinence

   Abstinence is only acceptable as true abstinence (i.e., when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a study, and withdrawal do not constitute abstinence.

b. Intrauterine device or intrauterine system
c. Oral contraceptive plus a barrier method
d. Diaphragm with vaginal spermicidal cream
e. Vaginal spermicide with a condom
f. Surgical sterilization (≥6 months postsurgery)

If a patient is usually not sexually active but becomes active, they, with their partner, must comply with the contraceptive requirements detailed above.

4.6.5 Sperm Donation

Male patients must agree not to donate sperm during the study and for at least 28 days after the last dose of study drug administration.

5 STUDY TREATMENTS AND MANAGEMENT

5.1 Description of Study Drug, Dose, and Administration

5.1.1 Description of Study Drug

Study drug is defined as miricorilant tablet, 150 mg or placebo for miricorilant tablet, 150 mg. Description of the study drug, including packaging and storage, is described in Table 1.

Table 1 Study Drug: Description, Packaging, and Storage

Specifications	Miricorilant	Placebo
Description	Miricorilant tablet, 150 mg is oval shaped and white to off-white in color. Each tablet contains 150 mg of miricorilant and the following inactive ingredients: methacrylic acid-methyl methacrylate copolymer, sodium lauryl sulfate, hypromellose acetate succinate, microcrystalline cellulose, croscarmellose sodium, silicon dioxide, and magnesium stearate.	Placebo for miricorilant tablet, 150 mg is designed to match the study drug in appearance. It is oval shaped and is white to off-white in color. Each tablet contains microcrystalline cellulose.
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.
Unit Dose Strength	Miricorilant tablet, 150 mg	Placebo for miricorilant tablet, 150 mg
Dose levels	600 mg and 900 mg	N/A
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
Dispensing study drug	Dispense to patients at the visits specified in Appendix A	Dispense to patients at the visits specified in Appendix A
Storage	Store as follows: • In a secure location • At 20°C–25°C (68°F–77°F), excursions permitted to 15°C–30°C (59°F–86°F) • Out of sight and reach of children	Store as follows: • In a secure location • At 20°C–25°C (68°F–77°F), excursions permitted to 15°C–30°C (59°F–86°F) • Out of sight and reach of children

Procedures for inventory, reconciliation, and destruction or return of study tablets are provided in Section 11.5.

5.1.2 Administration of Study Drug

Patients will be randomized in a 1:1:1 ratio to 600 mg miricorilant, 900 mg miricorilant or placebo. Study drug will be administered once daily, orally with 8 oz (240 mL) of water, along with food.

Patients will be instructed to take a total of 6 tablets at approximately the same time each day.

- Those in the 600 miricorilant group will take 4 miricorilant tablets and 2 placebo tablets.
- Those in the 900 miricorilant group will take 6 miricorilant tablets.
- Those in the placebo group will take 6 placebo tablets.

Patients who participate in the PK substudy must take the study drug in the mornings; these patients will be instructed to take their dose in the clinic during the Week 4 visit.

5.2 Non-Investigational Medicinal Agent

Not applicable.

5.3 Safety Assessments

5.3.1 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.

5.3.2 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 as a combination of 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 (including Baseline) and in the follow-up period. If excessive GR and/or MR antagonism is suspected, patients should discontinue the study medication, and administration of intravenous fluids, and intravenous or oral hydrocortisone should begin without delay and the actions outlined in Table 2 should be taken. The half-life of miricorilant is approximately 21 to 23 hours (Study CORT118335-850). Symptoms should continue to be monitored even after the last dose of study medication in the follow-up period.

5.4 Dose Modification

5.4.1 Dose Reduction

No dose reduction will be allowed.

5.4.2 Dose Interruption and/or Discontinuation: General Criteria

Treatment with study drug should be temporarily interrupted if deemed medically necessary by the Investigator. On interrupting treatment, the Investigator should notify the Corcept Medical Monitor.

Before restarting treatment with study drug, the Investigator must obtain approval from the Corcept Medical Monitor. If the event that necessitated treatment interruption recurs after study drug is restarted, the patient should be permanently discontinued from treatment.

In addition, patients will be permanently discontinued from treatment if they experience any of the criteria listed for stopping treatment with the study drug in Table 2.

5.4.3 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 Interruption or Discontinuation Due to Special Safety Events

Safety Event	Criteria for Interrupting and Restarting Study Drug and Patient Management	Criteria for Stopping Study Drug
Excessive GR or MR antagonism	Criteria: signs and symptoms of excessive GR and MR antagonism (Section 1.5) Management: • **Immediately interrupt miricorilant treatment** for ≥5 days and start standard supportive care, including intravenous fluids, as indicated. • If appropriate, administer supplemental glucocorticoids given in high doses to overcome the GR antagonism produced by miricorilant. Initially, consider intravenous hydrocortisone, followed by additional intravenous 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. • If the patient has been receiving treatment with a MR antagonist, consider discontinuing it, particularly in the presence of hypotension. • 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: fatigue, anorexia, nausea, and vomiting (associated with decreased oral intake), and abdominal pain.
Hypotension	Criteria: development of hypotension while on study drug. Management: • Confirm the diagnosis by in-office BP monitoring and orthostatic BP measurements. • Examine patient and check potassium levels. • If appropriate, advise the patient to hydrate orally with electrolyte containing hydration (e.g., Gatorade or Pedialyte). Hypotension can also be support with intravenous hydration with isotonic fluids • Patients who have hypotension should have any antihypertensive medications and diuretic medications discontinued as appropriate. • 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 intravenous 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 intravenous and oral hydration.

Safety Event	Criteria for Interrupting and Restarting Study Drug and Patient Management	Criteria for Stopping Study Drug
	• 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. Management: • Verify hyperkalemia and normal renal function • Obtain ECG for evaluation of hyperkalemia. • Interrupt miricorilant if hyperkalemia is severe (>6.0 mEq/L) or if renal function is impaired. • As medically indicated, initiate treatment for hyperkalemia. • 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 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. Underlying renal disease.
Suspected liver injury	Criteria: AST or ALT > 3 × ULN or total bilirubin > 2.0 × ULN while on study drug Management: • Repeat liver biochemistries (ALT, AST, alkaline phosphatase, total bilirubin) within 48 to 72 hours of results. • 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). • Obtain a history of exposure to environment chemical agents. • Rule out other causes of liver disease. • Obtain additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin). • 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. • Consider a gastroenterology or hepatology consultation.	Study drug will be stopped if: • ALT or AST > 5 × ULN. • ALT or AST > 3 × ULN and (TBL >2 × ULN or INR >1.5). • 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 Drug and Patient Management	Criteria for Stopping Study Drug
	• 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: • 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. • 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; MR, mineralocorticoid receptor; SBP, systolic blood pressure; TBL, total bilirubin level; ULN, upper limit of normal.

5.4.4 Pharmacokinetic Criteria for Dose Adjustment or Discontinuation

Not applicable.

5.5 Concomitant Medications

Administration of concomitant medications are at the discretion of the Investigator and/or the Corcept Medical Monitor.

5.5.1 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 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 drug. All medications (other than the study drug) administered 28 days of 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 treatment with study drug 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 treatment with study drug 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 for DDI.
Anxiolytic medication such as benzodiazepines	No restrictions unless there is a potential for DDI.

5.5.2 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

The Corcept Medical Monitor should be contacted in the case of any clarifications regarding concomitant therapy.

5.5.3 Prohibited Medications

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

- 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

5.6 Method of Study Drug Assignment and Randomization

All patients will be randomly assigned to the study drug (one of the 3 treatment groups) using a centralized interactive web response system (IWRS). Subject unique identifier creation and treatment allocation will be performed using the system. Randomization will be stratified by background antipsychotic medication (3 strata: olanzapine, risperidone or paliperidone, or quetiapine). 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 SoA (Appendix A).

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

5.7 Blinding/Unblinding

This is a double-blind, placebo-controlled study. Tablets (miricorilant,150 mg or placebo for miricorilant tablet, 150 mg) are 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 drug assignment. To maintain the overall quality and legitimacy of the clinical trial, unblinding should only occur in exceptional circumstances. These circumstances could include but are not limited to pregnancy of the patient or pregnancy of the patient's partner. The Corcept Medical Monitor must be notified before the blind is broken unless identification of the study drug is required for a medical emergency in which the knowledge of the specific blinded study

drug will affect the immediate management of the patient's condition (e.g., antidote available). In this case, the Sponsor 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.

Investigators wishing to discuss potential unblinding occurrences may contact the Corcept Medical Monitor for further discussion.

5.8 Dosing Diary

A dosing diary will be provided, and patients will be instructed to return all unused study tablets and the dosing diary at their visits. Patients should complete an entry in the diary for each self-administered dose of the study drug and note the names and doses of any concomitant medications taken. Entries will include the number of tablets and the date and time of the study drug administration. Time and dose administered should be documented in the clinic charts.

5.9 Study Drug Accountability and Treatment Adherence

Study drug adherence will be determined by review of the dose diary (Section 5.8) and counting returned tablets.

A patient who is assigned a study drug (i.e., to 600 mg miricorilant, 900 mg miricorilant or placebo, for 26 weeks of treatment) will be considered nonadherent if he or she misses >30% of the prescribed doses during the study, unless the patient's study drug 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 drug. 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.

5.10 Continued Access to Study Drug

There is no provision for continued access to study drug.

5.11 External Data Review Committee(s)

5.11.1 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 and in the conduct and monitoring of randomized clinical trials. The IDMC will meet at least quarterly. Further details describing the IDMC meeting frequency, 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 for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for 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 (Appendix A).

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 (see Section 4.3), 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 Demographics and Baseline Disease Characteristics

Patient demographic data, including age, sex, and race, and baseline disease characteristics will be documented at Screening.

6.3 Medical and Medication 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 Assessments

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 as indicated in the SoA (Appendix A).

If clinically significant abnormalities are observed during Screening, they should be reported in the patient's medical history; if observed any time after the first dose of study drug (Day 1), they will be considered TEAEs.

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 within 1–3 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 as indicated in the SoA (Appendix A). At Baseline, the 12-lead resting ECG (in triplicate) will be performed both before and after dosing.

Patients should be lying down resting for approximately 15 minutes before each ECG evaluation. A central reviewer will be used; instructions will be provided in the imaging manual.

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 the study drug. 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, cortisol, and aldosterone levels 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 (see Section 8.8). The Common Terminology Criteria for Adverse Events (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	Sodium	Drug screen
Hemoglobin	Potassium	
Hematocrit	Calcium	**Pharmacodynamic Biomarkers**
Mean corpuscular hemoglobin	Chloride	Adrenocorticotropic hormone (ACTH) (morning)
Mean corpuscular hemoglobin volume	Phosphorus	Serum cortisol (morning)
Mean corpuscular volume	Magnesium	Serum aldosterone
Platelet count	Creatinine	
Mean platelet volume	Bilirubin (total and direct)	**Pharmacokinetics**
Red blood cell distribution width	Albumin	Miricorilant
White blood cell count	Alkaline phosphatase	
White blood cell count with 5-part differential	Lactate dehydrogenase	**Other Biomarkers**
Neutrophils (percent and absolute)	Aspartate aminotransferase	Glucocorticoid-receptor activity
Lymphocytes (percent and absolute)	Alanine aminotransferase	
Monocytes (percent and absolute)	Glucose	**Pregnancy**
Eosinophils (percent and absolute)	Blood urea nitrogen	Serum/urine pregnancy test (for women of childbearing potential)
Basophils (percent and absolute)	Uric acid	
Lipid Panel	Bicarbonate	**Hormones**
Total cholesterol	Total protein	Follicle-stimulating hormone (FSH)
Direct low-density lipoprotein-cholesterol	Gamma-glutamyl transferase (GGT)	**Ad Hoc Testing**
High-density lipoprotein-cholesterol		Prothrombin time (PT)/ international normalized ratio (INR)
Very-low-density lipoprotein cholesterol	**Thyroid Function**	Activated partial thromboplastin time (aPTT)
Triglycerides (fasting only)	Thyroid-stimulating hormone (TSH)	Creatine kinase
Glycemic Parameters	Free thyroxine (T4)	Virus screen (hepatitis A, B, and C viruses)
Glycated hemoglobin (HbA1c)		Antinuclear antibodies (ANA)
Serum insulin (fasting)		Anti-smooth muscle antibodies (ASMA)
Plasma glucose (fasting)		Anti-liver-kidney microsome (anti-LKM)

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 as indicated in the SoA (Appendix A). Body weight will be measured without overcoat and shoes, and with only light clothing.

Waist circumference will be measured for all patients as indicated in the SoA (Appendix A). 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 autocalculated in electronic data capture (EDC) 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 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.

Miricorilant plasma concentration will be used to estimate relevant PK parameters, which will be reported as applicable (Table 5). PK data may also be used in safety and/or efficacy evaluations related to concerns arising during or after the study. Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Table 5 Pharmacokinetic Parameters to be Evaluated*

λ_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
CL/F	apparent oral clearance
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_{lag}	latest time after dosing before the first quantifiable concentration
t_{last}	time of the last quantifiable concentration
T_{max}	time to maximum concentration
V_{ss}/F	apparent oral volume of distribution at steady state

*This table does not contain a comprehensive list of PK parameters. The final list of PK parameters reported may exclude some of these parameters and/or include additional parameters.

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 the SoA (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 patients who do or do not have a high probability to benefit from treatment with miricorilant.

6.8 Other Assessments

6.8.1 Clinician Assessed Outcomes

The clinician assessed outcome assessments in the study include the BPRS, C-SSRS, CGI, and MINI. 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 MINI International Neuropsychiatric Interview for Psychotic Disorders is a brief structured interview for the major psychiatric disorders in DSM-5 and ICD-10.

6.8.2 Patient Reported Outcomes

Health-related quality of life scores will be measured using self-reported OWLQOL questionnaire and WRSM. Both the OWLQOL and the WRSM are intended to be administered together. The 17-item OWLQOL measures behavior and feelings that are associated with obesity and weight loss using a 7-point response scale that ranges from 0 "not at all" to 6 "a very great deal". The WRSM is a 20-item measure of the symptoms associated with obesity and obesity treatment, along with the degree to which each symptom "bothers the individual".

The questionnaires will be completed from Baseline until Follow-up and should always be conducted prior to dosing when conducted on study drug administration days.

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

An SoA is provided in Appendix A.

Corcept will be promptly notified of any protocol deviations.

The acceptable visit window during the Treatment Period for Day 1 through Week 8 visits is ±2 days and for Week 10 to Week 26 is ±5 days. 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 provide 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 is randomized to receive the study drug is 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 the Screening clinic visit (at least 8 hours).

The following Screening procedures will be performed:

- Obtain informed consent
- Record medical history
- Conduct MINI
- Record prior and concomitant medications
- Record AEs
- Record demographic information
- Perform urine drug test
- Measure height and body weight
- Perform physical examination
- Record vital signs (including orthostatic vital signs)
- Perform 12-lead resting ECG (in triplicate)
- Conduct psychological assessments (BPRS, C-SSRS, and CGI)
- Perform laboratory tests:
  - Hematology with platelet and WBC count 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 (HBV) screening

  - Hepatitis C (HCV) 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
- Measure body weight
- Measure waist circumference
- Measure hip circumference
- 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 ±1 hour)
  - Serum insulin (fasting)
  - Plasma glucose (fasting)
  - Serum cortisol (morning–8 AM ±1 hour)
  - Serum aldosterone
  - TSH
  - Free 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
- Other Biomarker Assessment:
  - Glucocorticoid-receptor activity marker
- Conduct psychological assessments (BPRS, C-SSRS, and CGI)
- Perform health related OWLQOL and WRSM questionnaires
- Provide dietary and exercise counseling
- Record any AEs
- Perform study randomization
- Dispense study drug; patient will take their first dose of the study drug in the clinic at this visit after clinic assessments

- Provide the patient with dose diary

7.3 Treatment Period

The following will be performed as indicated in the SoA, (Appendix A):

- Record any AEs
- Record concomitant medications
- Perform physical examination
- Measure body weight
- Measure waist circumference
- Measure hip circumference
- Record vital signs (including orthostatic vital signs)
- Perform 12-lead resting ECG (in triplicate)
- Conduct psychological assessments (BPRS, C-SSRS, and CGI)
- Perform health related OWLQOL and WRSM questionnaires
- Record unused study drug brought back by the patient
- Evaluate adherence to treatment based on returned dose diary and counting unused study drug

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

7.3.1 Week 2: Study Day 15 (±2 days)

- Perform assessments listed in Section 7.3
- Dispense study drug
- Perform laboratory tests:
  - Chemistry panel
  - Hematology with platelet and WBC differential

7.3.2 Week 4: Study Day 29 (±2 days)

- Perform assessments listed in Section 7.3
- Dispense study drug
- Perform laboratory tests:
  - Chemistry panel
  - Hematology with platelet and WBC differential
  - Urine pregnancy test (women of child-bearing potential); if urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test

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 drug on 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.

7.3.3 Week 6: Study Day 43 (±2 days)

- Perform assessments listed in Section 7.3
- Dispense study drug
- Perform laboratory tests:
  - Chemistry panel
  - Hematology with platelet and WBC differential

7.3.4 Week 8: Study Day 57 (±2 days)

- Record any AEs
- Record concomitant medications
- Measure body weight
- Record unused study drug brought back by the patient
- Evaluate adherence to treatment based on returned dose diary and counting unused study drug
- Perform laboratory tests:
  - Chemistry panel

7.3.5 Week 10: Study Day 71 (±5 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
- Dispense study drug
- Perform laboratory tests:
  - Chemistry panel (fasting)
  - Hematology with platelet and WBC differential
  - Lipid panel (fasting)
  - Urine pregnancy test (women of child-bearing potential); if urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test

7.3.6 Week 12: Study Day 85 (±5 days)

- Record any AEs
- Record concomitant medications
- Measure body weight
- Record unused study drug brought back by the patient
- Evaluate adherence to treatment based on returned dose diary and counting unused study drug
- Perform laboratory tests:
  - Chemistry panel

7.3.7 Week 14: Study Day 99 (±5 days)

- Perform assessments listed in Section 7.3

- Dispense study drug
- Perform laboratory tests:
  - Chemistry panel
  - Hematology with platelet and WBC differential
  - HbA1c
  - Urine pregnancy test (women of child-bearing potential); if urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test
- Provide a refresher on dietary and exercise counseling on weight loss

7.3.8 Week 16: Study Day 113 (±5 days)

- Record any AEs
- Record concomitant medications
- Measure body weight
- Record unused study drug brought back by the patient
- Evaluate adherence to treatment based on returned dose diary and counting unused study drug
- Perform laboratory tests:
  - Chemistry panel

7.3.9 Week 18: Study Day 127 (±5 days)

- Perform assessments listed in Section 7.3
- Dispense study drug
- Perform laboratory tests:
  - Chemistry panel
  - Hematology with platelet and WBC differential
  - Urine pregnancy test (women of child-bearing potential); if urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test

7.3.10 Week 19: Study Day 134 (±5 days)

- Record any AEs
- Record concomitant medications
- Perform laboratory tests:
  - Chemistry panel
  - Hematology with platelet and WBC differential

7.3.11 Week 20: Study Day 141 (±5 days)

- Record any AEs
- Record concomitant medications
- Measure body weight
- Record unused study drug brought back by the patient
- Evaluate adherence to treatment based on returned dose diary and counting unused study drug

- Perform laboratory tests:
  - Chemistry panel
  - Hematology with platelet and WBC differential

7.3.12 Week 21: Study Day 148 (±5 days)

- Record any AEs
- Record concomitant medications
- Perform laboratory tests:
  - Chemistry panel
  - Hematology with platelet and WBC differential

7.3.13 Week 22: Study Day 155 (±5 days)

- Perform assessments listed in Section 7.3
- Dispense study drug
- Perform laboratory tests:
  - Chemistry panel
  - Hematology with platelet and WBC differential
  - Urine pregnancy test (women of child-bearing potential); if urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test

7.3.14 Week 23: Study Day 162 (±5 days)

- Record any AEs
- Record concomitant medications
- Perform laboratory tests:
  - Chemistry panel
  - Hematology with platelet and WBC differential

7.3.15 Week 24: Study Day 169 (±5 days)

- Record any AEs
- Record concomitant medications
- Measure body weight
- Record unused study drug brought back by the patient
- Evaluate adherence to treatment based on returned dose diary and counting unused study drug
- Perform laboratory tests:
  - Chemistry panel
  - Hematology with platelet and WBC differential

7.3.16 Week 25: Study Day 176 (±5 days)

- Record any AEs
- Record concomitant medications

- Perform laboratory tests:
  - Chemistry panel
  - Hematology with platelet and WBC differential

7.3.17 Week 26: Study Day 183 (±5 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 ±1 hour)
  - Serum cortisol (morning–8 AM ±1 hour)
  - Serum aldosterone
  - TSH
  - Free T4
  - HbA1c
  - Urine pregnancy test (women of child-bearing potential); if urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test
- Other Biomarker Assessment:
  - 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 (26 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 returned dose diary and counting unused study drug
- Perform physical examination
- Measure body weight
- Measure waist circumference
- Measure hip circumference

- 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 ±1 hour)
  - Serum cortisol (morning–8 AM ±1 hour)
  - Serum aldosterone
- Other Biomarker Assessment:
  - Glucocorticoid-receptor activity marker
- Conduct psychological assessments (BPRS, C-SSRS, and CGI)
- Perform health related OWLQOL and WRSM questionnaires

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

For patients who complete 26 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
- Measure waist circumference
- Measure hip circumference
- 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 (BPRS, C-SSRS, and CGI)
- Perform health related OWLQOL and WRSM questionnaires

7.6 Telephone Follow-Up Assessment of Survival

Not applicable.

7.7 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. All SAEs must be reported to the Sponsor within 24 hours from awareness of the event.

The Investigator (or medically qualified designee) is responsible for determining whether an AE is clinically/medically significant. All available information regarding the AE must be documented on the eCRF (or in the patient's medical record).

8.2 Monitoring Safety Data During the Study

Safety results collected during the study (e.g., AEs, laboratory results, physical findings) will be monitored on an ongoing basis by the Corcept Medical Monitor and the Investigator. All abnormal laboratory results, and 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 laboratory results, and ECG and vital-signs findings. All Grade 3 and above findings will immediately be reported to the Corcept Medical Monitor within 24 hours.

The Sponsor or its designee will promptly evaluate all reported safety information against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators and applicable regulatory authorities. Investigators, in turn, are responsible for notifying their IRB of new safety findings according to their local requirements.

In addition, an IDMC will be established to conduct periodic reviews of data to ensure the safety of patients (see Section 5.11).

8.3 Definition of an Adverse Event

An AE is defined as any unfavorable or unintended sign (including an abnormal laboratory finding that is inconsistent with the patient's baseline findings), symptom, or disease (new or exacerbated) temporally associated with the use of a study drug, whether considered related to the study drug or not.

Examples of AEs include:

- New conditions recorded after signing the ICF.
- Worsening of a chronic or intermittent pre-existing condition, including an increase in severity, frequency, duration, and/or has an association with a significantly worse outcome.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either the study drug or a concurrent medication.

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 defined as any untoward medical occurrence that, at any dose:

- Results in death.
- Is in the opinion of the Investigator immediately life threatening (i.e., the patient is at immediate risk of death; it does not include a reaction that, had it occurred in a more severe form, might have caused death).
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization. [a]
- Results in persistent or significant disability or incapacity. [b]
- Is a congenital anomaly or birth defect.
- Is an important medical event that may not be immediately life-threatening, result in death, or require hospitalization, but based on appropriate medical judgment, it jeopardizes the patient, or may require medical or surgical intervention to prevent one of the outcomes listed.

[a] In general, hospitalization signifies that the patient was admitted to the hospital for observation and/or treatment (usually involving at least an overnight stay) that would not have been appropriate in the physician's office or in an outpatient setting.

[b] The term disability means a substantial disruption of a person's ability to conduct normal life functions (or substantially different from their pre-treatment, baseline functional abilities). This definition is not intended to include experiences of relatively uncomplicated influenza and accidental trauma (e.g., a sprained ankle) that may interfere or prevent everyday life functions, but do not constitute substantial disruption.

The following are NOT considered SAEs:

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from the patient's baseline.
- Hospitalization for social/convenience considerations.
- Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience.

The Investigator should institute any clinically necessary supplementary investigation of SAE information. In the case of patient death, any post-mortem findings/reports will be requested.

8.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A suspected unexpected adverse reaction is a serious adverse reaction that is both unexpected, i.e., not present in the product's Reference Safety Information (RSI) and meets the definition of an SAE, the specificity or severity of which is not consistent with those specifically noted in the RSI.

8.6 Expectedness

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

8.7 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.

8.8 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 modification 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. All Grade 3 and above findings will immediately be reported to the Corcept Medical Monitor within 24 hours.

8.9 Documentation of Adverse Events

Patients will be evaluated and questioned to identify AEs during the study. Grade 3 and above AEs are to be reported to the Sponsor as soon as the Investigator becomes aware.

Collection of AEs will start immediately following signing of the ICF and will continue throughout the study (including the 28 day Follow-up period) as noted in the SoA (Appendix A). AEs that occur after start of study treatment following randomization to the study drug and up to and including 28 days after administration of the last dose of the study drug will be considered TEAEs. Any AEs reported more than 28 days after the last dose of study drug will be considered posttreatment AEs.

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).

If 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 that are drug-related and unexpected (not specified in the RSI section of the Investigator's Brochure) or if the event is of greater severity or frequency than that described in the Investigator's Brochure) must be reported to the governing IRB and governing health authorities as required.

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 8.10.1), (4) relationship to the study drug (see Section 8.10.2), (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 the study drug. Adverse events (including lab abnormalities that constitute AEs) should be described using a unifying diagnosis whenever possible, rather than individual underlying signs and symptoms.

8.10 Adverse Event Classification

8.10.1 Intensity Grades of Adverse Events

The seriousness and severity of an AE are different assessments. 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 6 should be used to evaluate the grade of severity for the AE.

Table 6 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).

8.10.2 Assessment of Causality: Relationship of Adverse Event to Study Drug or Study 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 7. The Investigator's assessment of causality must be provided for all AEs (serious and nonserious) as required for safety reporting to health authorities.

Alternative causes, such as the natural history of the underlying disease(s), concomitant therapy, other risk factors, and the temporal relationship of the AE or SAE to the study drug should be considered and investigated.

There may be situations when an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is critical that the Investigator assesses causality for every SAE prior to the transmission of the SAE report to the Sponsor, since the causality assessment is one of the criteria used when determining regulatory reporting requirements. The Investigator may change his/her opinion of causality in light of follow-up information received, amending the SAE report accordingly.

Several factors should be considered in making this assessment, including:

- Temporal relationship of the AE to the administration of the study treatment/study procedure.
- Whether an alternative etiology has been identified.
- Mechanism of action of the study drug.
- Biological plausibility.

Table 7 Causal Attribution Guidance for Adverse Events

Not related to study drug	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 drug. The cause must be noted on the AE eCRF.
Possibly related to study drug	An AE that might be due to the use of the drug. 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 drug	An AE that might be due to the use of the drug. The relationship in time is suggestive. An alternative explanation is less likely, e.g., concomitant drug(s) or concurrent disease(s).
Related to study drug	An AE that is due to the use of the drug.

8.11 Procedures for Reporting a Serious Adverse Event

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

SAE reporting details are provided below:

[redacted]

8.12 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 8.9 and 8.11, 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.

8.13 Recording Disease Progression

Not applicable.

8.14 Recording Deaths

When recording a death as an SAE, the AE that caused or contributed to the fatal outcome should be recorded as a single medical concept. If the cause of death is unknown and cannot be ascertained at the time of the reporting, record as "unexplained death".

8.15 Adverse Event Follow-up

All AEs considered to be related to the study drug (see Section 8.10.2 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. Responses to follow-up queries about the reported event(s) should be recorded and reported to the Sponsor as soon as possible.

8.16 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to the Sponsor during the study and within 28 days of the last dose of the study drug(s).

8.16.1 Maternal Exposure

If a patient becomes pregnant during the study, study drug should be discontinued immediately. Pregnancy itself is not regarded as an AE unless there is a suspicion that the study drug 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 study drug, 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 managed as SAEs. Elective abortions without complications should not be considered 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 the pregnancy, even if the patient discontinued the study.

The Investigator or designee should ensure that all relevant information is provided to the responsible Clinical Safety Group All pregnancy outcomes must be reported by the Investigator within 24 hours after he or she becomes aware of it.

8.16.2 Paternal Exposure

Pregnancy of the patient's partner is not considered 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 of study drug should be followed and documented; live births resulting from these pregnancies may be followed for up to two months after delivery.

8.17 Treatment of Overdose

There is currently no experience with overdose of miricorilant. For monitoring symptoms of excessive GR and MR antagonism, refer to Section 5.4.3.

8.18 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 the study drug), study site personnel will apply appropriate medical intervention according to current standards of care and contact the Corcept Medical Monitor.

9 STATISTICAL METHODS

9.1 Analysis Populations

The analysis populations are defined in Table 8.

Table 8 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 drug.
Modified Intent-to-Treat (mITT) Population [a]	All patients who receive at least 1 dose of study drug.
Efficacy Evaluable (EE) Population	All patients who receive 4 weeks of study drug and have Baseline and at least 1 body weight measurement taken on or after Week 4.
PK Population	All patients who have evaluable PK data.

Abbreviations: PK, pharmacokinetics.
a. An Intent-to-Treat (ITT) Population is defined as all patients who are randomized into the study even if they do not receive any study drug. The mITT Population includes all randomized patients who start study drug.

Summaries of demographics and baseline conditions will be done for the 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 may also be performed on the Modified Intent-to-Treat (mITT) 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 Statistical Analyses

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.

9.3 Hypothesis Testing

Evaluating the primary objective entails comparing each of the 2 miricorilant treatment groups independently to placebo on the primary endpoint, the change in body weight from Baseline to Week 26. For each test, the null hypothesis is that there is no difference between miricorilant and placebo in change in body weight. The alternative hypothesis is that there is a difference between groups. Each of the 2 hypotheses will be assessed at a 2-sided α=0.05 significance level with no adjustment to α for multiplicity.

9.4 Sample Size Calculation

The planned sample size is 150 subjects randomized 1:1:1 across 2 miricorilant treatment groups and 1 placebo group.

Fifty patients per group will ensure at least 90% power to detect a difference of 5 kg in mean change from Baseline in body weight between placebo and either miricorilant treatment group. These calculations assume a common standard deviation of 6 kg and a 0.05 two-sided significance level two-sample z-test. A drop-out rate of 40% from Baseline to Week 26 is assumed in this calculation.

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

Randomization will be stratified by the type of antipsychotic medication used (one stratification factor with 3 levels). If ≥20 patients complete 26 weeks of treatment (10 patients treated with miricorilant and 10 patients treated with placebo) in one of the allowed antipsychotic medication groups (olanzapine, risperidone or paliperidone, or quetiapine), this sample size provides 60% power to detect a difference in body weight change of 5 kg between the miricorilant and placebo groups, at alpha=0.1 level for that antipsychotic medication. The sample size estimates have not been adjusted for multiple comparisons.

9.5 Analysis Plan

9.5.1 Patient Disposition

Patient disposition summaries will include the number of enrolled patients, the number of patients in each analysis population, the number of patients who complete the study, and the number of patients who terminate the study early broken out by the primary reason for discontinuation.

9.5.2 Demographic and Baseline Data

Categorical demographic and baseline data will be summarized by frequency while continuous variables will be summarized by mean, standard deviation, median, minimum, and maximum. Summarizes will be presented by treatment group and for all patients combined.

9.5.3 Prior and Concomitant Medications

Verbatim terms will be mapped to Anatomical Therapeutic Chemical class and Generic Drug Names using the most current version of the World Health Organization Drug Dictionary. The number and percentage of patients will be presented for each medication by treatment group and for all patients combined.

9.5.4 Analysis of the Primary Efficacy Endpoints

The primary efficacy endpoint is based on the change in body weight from Baseline to Week 26. The primary analysis will use a mixed-effect model with repeated measures (MMRM) with change in body weight at each visit as the outcome variable; baseline body weight as a covariate; and antipsychotic medication (stratification factor), randomized treatment (600 mg or 900 mg miricorilant or placebo), visit, and treatment-by-visit interaction as fixed effects. The difference in body weight change at Week 26 between each miricorilant treatment group and placebo will be estimated from the model along with its associated 95% confidence interval (CI).

The primary efficacy analysis will use the Efficacy Evaluable population. Neither CIs nor p-values will be adjusted for multiplicity.

9.5.5 Approach to Missing Data Analysis

Sensitivity analyses will be specified in the SAP.

9.5.6 Analysis of the Secondary Efficacy Endpoints

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

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 as a covariate, and antipsychotic medication (stratification factor) and randomized treatment as fixed effects, will be used to compare each miricorilant dose group to placebo.

Waist-to-hip ratio will be analyzed using similar models as the primary analysis of weight change. Differences between each miricorilant dose group and placebo will be estimated along with corresponding 95% CIs. Waist-to-hip ratio data may require a log-transformation prior to analysis.

9.5.7 Analyses of Exploratory Efficacy Endpoints

The relationship between background antipsychotic medication and efficacy will be explored through subgroup analyses. Specifically, 3 MMRM analyses will be performed, one for each subgroup of patients taking olanzapine, risperidone or paliperidone, or quetiapine. Each MMRM will be similar to the primary analysis except all miricorilant dose groups will be combined into a single treatment group. Each model will use change in body weight at each visit as the outcome variable; Baseline body weight as a covariate; and treatment (miricorilant or placebo), visit, and

treatment-by-visit interaction as fixed effects. For each background medication, the difference in body weight change at Week 26 between the combined miricorilant dose groups and placebo will be estimated from the appropriate model along with its associated 95% CI and p-value.

Analyses of continuous endpoints assessed at multiple post-treatment timepoints, such as the change in BPRS, CGI, OWLQOL, and WRSM from Baseline to Week 26 will be analyzed using models similar to the primary analysis of body weight change. C-SSRS results will be summarized descriptively. Endpoints like ACTH, serum cortisol, and serum aldosterone that are measured only at Baseline and Week 26 will be assessed using analysis of covariance (ANCOVA) models that include the change in the endpoint between Baseline and Week 26 as the outcome variable, baseline body weight as a covariate, and antipsychotic medication and randomized treatment as factors. 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.

HOMA-IR will be analyzed using similar models as the primary analysis of weight change. Differences between each miricorilant dose group and placebo will be estimated along with corresponding 95% CIs. HOMA-IR data may require a log-transformation prior to analysis

Dose response will be evaluated using an MMRM identical to that used for the primary analysis except that the placebo group will not be included. The difference between the miricorilant dose groups in the change in body weight at Week 26 will be estimated from the model using a linear contrast. The difference will be accompanied by an associated 95% CI and p-value.

9.5.8 Safety Analyses

Adverse events will be mapped to system organ classes and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). TEAEs will be summarized overall and displayed by system organ class and preferred term, as well as by severity, seriousness, and relationship to the study drug. Serious AEs and AEs that lead to study drug 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.

9.5.9 Pharmacokinetic Analysis

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.

Details of the PK analyses will be described in a PK analysis plan finalized before database lock.

9.5.10 Pharmacogenetic Analysis

Not applicable.

9.5.11 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 or local regulations. The protocol, IB, ICFs, recruitment materials, and all patient materials will be submitted to the IRB for review and approval. Approval of the clinical trial must be obtained before any patient is enrolled, and the Investigator must submit written approval to the Sponsor before enrolling any patient.

The Investigator is responsible for ensuring annual reviews by the IRB occur, and that they receive approval. The Investigator is also responsible for informing the IRB of any amendment to the protocol in accordance with local requirements before implementing any changes.

Any changes to the ICF must be approved by the IRB. A determination will be made as to whether previously consented patients need to be re-consented. Other documents related to the clinical trial may also need IRB approvals prior to implementing.

The Sponsor or their designee 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 retained and provided to the Sponsor or their designee.

Progress reports and notifications, including required safety information, 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 must be obtained from each patient before initiating any study-mandated screening procedures, or enrollment into the study. The ICF will contain all of the elements required by ICH guidelines for GCP and any additional elements required by local regulations.

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 informed consent process discussion should be documented in patient's record.

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

The ICF should include information about possible retention of biological samples at the conclusion of this study, the purpose of retaining the samples and the time period for which they will be retained. With the patient's permission, samples, including blood, plasma, serum, and tissue, may be retained for

- Future identification of biomarkers of disease or miricorilant treatment.
- Future analysis of active metabolite concentrations and possible biomarkers related to drug response.

10.3.2 Patient Confidentiality

To maintain patient confidentiality, all source documents, study reports, and communications will identify the patient by the assigned patient number.

The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee, the IRB and regulatory authority access to the patient's original source records for data verification and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by applicable laws and regulations.

10.3.3 Patient Privacy

Before enrollment into the study, the Investigator or designee must explain to each patient that their personal information will be shared with the Sponsor and companies working with the Sponsor, as well as shared with regulatory agencies and the IRB. Personal information is shared to ensure the study is being conducted properly, to evaluate the study results, and to develop and approve the study drug if it is shown to be safe and effective.

It is the Investigator's (or designee's) responsibility to obtain the patient's written acknowledgement or written permission to use their personal information per country-specific regulations. This must be obtained before initiating any study-mandated procedures or enrollment into the study.

If the patient withdraws permission to use their personal information, it is the Investigator's responsibility to, 1) document the patient's request to withdraw (i.e., as a written request), 2) ensure that no further data will be collected from the patient, and 3) ensure that the patient will be removed from the study.

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Quality Management

As part of quality management based on a risk-based approach per ICH E6(R2): risk reduction activities may be incorporated in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to standard operating procedures, and training in processes and procedures.

Predefined quality tolerance limits should be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact subject safety or reliability of trial results. Detection of deviations from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed.

Study sites, the study database, and study documentation will be monitored regularly and may be subject to a quality assurance (QA) audit during the study by the IRB and/or the Sponsor or its designee. In addition, inspections may be conducted by regulatory agencies at their discretion.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC 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 SOPs and the study-specific monitoring plan, the monitors will verify that the clinical study is conducted, data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices, Good Manufacturing Practices).

Upon request, the investigational site will provide direct access and allow the Sponsor (or its representative including monitor), IRB and regulatory authorities to review and inspect all trial related sites, drug storage area, study-drug stock, drug accountability records, patient charts, source documents, and other records related to study conduct.

The Investigator should contact the Sponsor or their designee immediately if contacted by a regulatory agency regarding an inspection.

11.2 Study Monitoring

The Sponsor or designee will be responsible for the monitoring of the study. Study monitors will contact and visit the Investigators at regular intervals throughout the study to answer study questions, and to systematically and independently examine all study-related activities, verify adherence to the protocol, and assess the completeness, consistency, and accuracy of the data.

Monitoring may include, but is not limited to:

- Reviewing eCRFs for accuracy and completeness.
- Assessing compliance with the protocol and adherence to regulatory and GCP requirements
- Verifying that the site maintains an adequate supply of study drugs, any necessary supplies, and that appropriate storage conditions are maintained.

Monitoring visits will be conducted according to the ICH Guideline for GCP and all applicable country and local regulations and guidance.

By agreeing to participate in this research study, the Investigators agree to co-operate with the study monitor to ensure that any problems detected during the monitoring visits are promptly resolved.

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

11.3 Documentation

11.3.1 Source Documentation

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, clinic charts, the Investigator's patient study files, results of diagnostic tests, including x-rays, laboratory tests and ECGs). All source data should be attributable, legible, contemporaneous, original, accurate, and completed. Changes to source data should be traceable (i.e., dated and initialed), 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.

11.3.2 Case Report Forms

The Investigator must generate and maintain complete, adequate, accurate, reliable, and legible records in a timely manner to enable full documentation of study conduct. All data entered into CRFs (paper or electronic) must be substantiated by and consistent with a source document.

Discrepancies between CRFs and their respective source documents should be explained. All changes in eCRF data entry at the study site will be performed by designated site personnel and will be in the clinical database audit trail. In the event paper CRFs are utilized, any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry.

All changes in CRF data entry at the study site will be performed by designated site personnel.

11.3.3 Retention of Study Essential Documents

The Investigator must retain adequate and accurate records so that study conduct can be fully documented and the study data to be subsequently verified.

Study essential documents, which include the patient identification code list (i.e., patient names and corresponding study numbers), 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 study drug. 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 the Sponsor, if applicable. If the Investigator can no longer maintain the records, it is the responsibility of the Investigator to contact the Sponsor. These documents may be transferred to another responsible party, acceptable to the Sponsor, who agrees to abide by the retention policies. Written notification of transfer must be submitted to the Sponsor. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

11.3.4 Sample Collection, Preparation, and Shipping

Instructions for collection, preparation, and shipping of all laboratory samples will be provided in the study laboratory manual.

11.4 Long-Term Retention of Biological Samples

All biological samples will be retained by the Sponsor or designee under the original informed consent of the patient and the IRB approval. Samples will be held for a period up to 15 years after completion of the clinical study report. The Sponsor or the designee may store the patient's sample(s) longer if required to address regulatory agency questions; in this event, the patient's sample(s) will be destroyed after all questions are adequately answered.

An individual patient can choose to withdraw consent to have his/her samples used for future research at any time without affecting their participation in the study, or their care by the health provider. After receipt of a request for sample destruction, that patient's sample(s) will then no longer be used for future research purposes beyond the current study, and their sample(s) will be destroyed. However, if there are ongoing regulatory questions, the patient's sample(s) will be destroyed after all questions are adequately answered.

The long-term retention samples will be coded to allow de-identification according to applicable regulatory guidelines. It is the responsibility of the trial site to ensure that samples are appropriately labelled in accordance with trial procedures to comply with all applicable laws.

Biological samples collected from participants as part of this trial will be transported, stored, accessed, and processed in accordance with all applicable laws relating to the use and storage of human tissue for research purposes.

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/government health authorities and study procedures. Storage of study drug is described in Table 1.

11.5.2 Clinical-Supply Inventory

Each clinical site is required to complete and maintain a detailed inventory 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 their designee must provide an explanation for any destroyed or missing study drug or study materials.

The Investigator or their 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 their designee must retain all unused or expired study supplies until the study monitor (on-site clinical research associate) has confirmed the accountability data and Sponsor has approved return or destruction.

11.5.3 Return or Destruction of Study Drug and/or Supplies

At the end of the study, after final drug-inventory reconciliation by the study monitor, the study site will either return study drug and/or supplies to the Sponsor or designee, or destroy all unused study drug and/or supplies, including empty containers, according to institutional policy.

11.5.4 Study Drug Destroyed by the Site

Unused/undispensed study drug and/or supplies may be destroyed on site, per the site's SOPs, but only after Sponsor has granted approval for drug destruction. The study monitor must account for all study drug in a formal reconciliation process, before study-drug destruction.

Any destruction of study drug on site must be documented. Documentation must be provided to the Sponsor and retained in the Investigator study files.

11.5.5 Study Drug Returned to Sponsor for Destruction

If a site is unable to destroy unused/undispensed study drug and/or supplies appropriately, the site can request return of study drug and/or supplies to the Sponsor or designee.

The return of study drug and/or supplies must be accounted for on a Study Drug Return Form provided by the Sponsor or designee

11.5.6 Drug Accountability

It is the responsibility of the Investigator to maintain drug accountability at the study site and ensure that a current record of study-drug disposition is maintained. It is the responsibility of the Investigator to ensure that the study drug 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, lost, or accidentally or deliberately destroyed study product.

Dispensing records will document quantities received from the Sponsor (or designee) and quantities dispensed to patients, including lot number, date dispensed, patient identifier number, patient initials, the initials of the person dispensing the drug, quantities of drug returned by the patients and disposal/return of returned study drug.

11.6 Post-Trial Care

There is no provision for continued access to study drug (Section 5.10).

11.7 Protocol Noncompliance

A protocol deviation is any noncompliance with requirements in the clinical-trial protocol, GCP, or the manual of procedures (MOP). The noncompliance may be on the part of the patient, the Investigator, or the study-site staff. As a result of deviations, corrective actions consistent with ICH E6(R2) may be implemented.

Prospective approval of deviations from the inclusion and exclusion criteria, known as protocol waivers or exemptions are not permitted. Changes to the conduct of the protocol may not be made, except to address an immediate risk to the subject, unless the change has been submitted to the regulatory authorities for review and the change has been approved by the IRB.

Sponsor clinical-study staff and contractors may acknowledge, but not approve, protocol deviations reported by a site that have happened or are planned to happen.

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

After the protocol is approved by the Sponsor and by IRBs, any change that might affect the approval of the IRBs must be documented in the form of a protocol amendment. The amended protocol must be approved by the IRB and annually, as local regulations require.

11.8 Financial Disclosure

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

11.9 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 the Sponsor. The Investigator agrees to submit all manuscripts or abstracts to the Sponsor for review before submission to the publisher.

The Sponsor 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 (ICMJE) requirements.

11.10 Electronic Systems

All electronic systems, including clinical study sites, clinical operations, data management, biostatistics, safety, and CRO systems, etc., used to collect, manage, and store study data should be validated and in compliance with 21 CFR Part 11. The validation documentation should be made available at all times during inspection or Sponsor audits. Any modification to the validated system should be documented via a quality change control process and justified to their intended use.

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13 APPENDICES

Appendix A: Schedule(s) of Activities

Table 9 Schedule of Activities

			Treatment Period																		
			Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	Week 18	Week 19	Week 20	Week 21	Week 22	Week 23	Week 24	Week 25	Week 26		Follow-Up 28±5 days after last dose of study drug
Assessment	**Screening Days −28 to −1**	**Baseline Day 1**	**Day 15 ±2 days**	**Day 29 ±2 days**	**Day 43 ±2 days**	**Day 57 ±2 days**	**Day 71 ±5 days**	**Day 85 ±5 days**	**Day 99 ±5 days**	**Day 113 ±5 days**	**Day 127 ±5 days**	**Day 134 ±5 days**	**Day 141 ±5 days**	**Day 148 ±5 days**	**Day 155 ±5 days**	**Day 162 ±5 days**	**Day 169 ±5 days**	**Day 176 ±5 days**	**Day 183 ±5 days**	**ET [a]**	
Informed consent [b]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Inclusion/ exclusion criteria [b]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Medical history and prior medications [c]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Concomitant medications	X	X	X	X	X	X	X	X	X	X	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	X	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
FSH test [e]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Urine drug test	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Diet and exercise counseling	-	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 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	Week 18	Week 19	Week 20	Week 21	Week 22	Week 23	Week 24	Week 25	Week 26		
			Day 15 ±2 days	Day 29 ±2 days	Day 43 ±2 days	Day 57 ±2 days	Day 71 ±5 days	Day 85 ±5 days	Day 99 ±5 days	Day 113 ±5 days	Day 127 ±5 days	Day 134 ±5 days	Day 141 ±5 days	Day 148 ±5 days	Day 155 ±5 days	Day 162 ±5 days	Day 169 ±5 days	Day 176 ±5 days	Day 183 ±5 days		
Physical examination [f]	X	X	X	X	X	-	X	-	X	-	X	-	-	-	X	-	-	-	X	X	X
Body weight [g]	X	X	X	X	X	X	X	X	X	X	X	-	X	-	X	-	X	-	X	X	X
Height [g]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Vital signs (including orthostatic vital signs)	X	X	X	X	X	-	X	-	X	-	X	-	-	-	X	-	-	-	X	X	X
12-lead resting ECG (in triplicate) [h]	X	X	X	X	X	-	X	-	X	-	X	-	-	-	X	-	-	-	X	X	X
Waist and hip measurements [i]	-	X	X	X	X	-	X	-	X	-	X	-	-	-	X	-	-	-	X	X	X
Dispensing of study drug (tablets)	-	X	X	X	X	-	X	-	X	-	X	-	-	-	X	-	-	-	-	-	-
Accounting of unused tablets	-	-	X	X	X	X	X	X	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	X	-	X	-	X	-	X	-	X	X	-
Virus screen (HCV, HBV)	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 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	Week 18	Week 19	Week 20	Week 21	Week 22	Week 23	Week 24	Week 25	Week 26		
			Day 15 ±2 days	Day 29 ±2 days	Day 43 ±2 days	Day 57 ±2 days	Day 71 ±5 days	Day 85 ±5 days	Day 99 ±5 days	Day 113 ±5 days	Day 127 ±5 days	Day 134 ±5 days	Day 141 ±5 days	Day 148 ±5 days	Day 155 ±5 days	Day 162 ±5 days	Day 169 ±5 days	Day 176 ±5 days	Day 183 ±5 days		
Hematology with platelet and WBC differential	X	X	X	X	X	-	X	-	X	-	X	X	X	X	X	X	X	X	X	X	X
Chemistry [j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lipid panel [k]	X	X	-	-	-	-	X	-	-	-	-	-	-	-	-	-	-		X	X	X
HbA1c	X	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±1 hour) [l]	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X	-
Serum cortisol (morning–8 AM±1 hour) [l]	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X	-
Serum aldosterone [l]	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X	-
Glucocorticoid-receptor activity marker	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X	-
MINI	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
BPRS	X	X	X	X	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 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	Week 18	Week 19	Week 20	Week 21	Week 22	Week 23	Week 24	Week 25	Week 26		
			Day 15 ±2 days	Day 29 ±2 days	Day 43 ±2 days	Day 57 ±2 days	Day 71 ±5 days	Day 85 ±5 days	Day 99 ±5 days	Day 113 ±5 days	Day 127 ±5 days	Day 134 ±5 days	Day 141 ±5 days	Day 148 ±5 days	Day 155 ±5 days	Day 162 ±5 days	Day 169 ±5 days	Day 176 ±5 days	Day 183 ±5 days		
C-SSRS	X	X	X	X	X	-	X	-	X	-	X	-	-	-	X	-	-	-	X	X	X
CGI	X	X	X	X	X	-	X	-	X	-	X	-	-	-	X	-	-	-	X	X	X
OWLQOL/ WRSM	-	X	X	X	X	-	X	-	X	-	X	-	-	-	X	-	-	-	X	X	X
PK substudy [m]	-	-	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Abbreviations: ACTH, adrenocorticotropic hormone; AE, adverse event; BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impression; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; ET, early termination; FSH, follicle-stimulating hormone; HbA1c, glycated hemoglobin; ICF, informed consent form; MINI, Mini International Neuropsychiatric Interview; OWLQOL, Obesity Weight Loss Quality of Life Scale; PK, pharmacokinetic; T4, thyroxine; TSH, thyroid-stimulating hormone; WBC, white blood cell (count); WRSM, weight-related symptom measure.

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. BMI will be autocalculated from the EDC database based on height and weight measurements.
h. At Baseline, the 12-lead resting ECG (in triplicate) will be performed both before dosing and 2 hr ±15 min after dosing.
i. Waist-to-hip ratio will be autocalculated from the EDC database based on waist and hip measurements.
j. Fasting chemistry panels will occur at Screening, Baseline, Week 10, Week 26, and ET. All other chemistry panels will be done nonfasting.
k. Lipid panel to include cholesterol, direct low-density lipoprotein (LDL), very-low-density LDL (VLDL) and high-density lipoprotein (HDL). Fasting lipid panels to include triglycerides will occur at Screening, Baseline, Week 10, Week 26, and ET.
l. ACTH and serum cortisol tests will be completed in the morning–8 AM ±1 hour).

m. 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 drug on 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 09 June 2022 compared with the Amendment 4 dated 11 January 2022 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.

A significant revision to the protocol is:

- Addition of study visits at Weeks 19, 21, 23 and 25 during the treatment period to increase safety monitoring of remaining patients on the study for any changes in reported AEs, concomitant medications, and to their laboratory values.
  - Chemistry panel and hematology with platelet and WBC differential testing will be performed at every week at these visits.
- For clinic visits at Weeks 20 and 24, additional laboratory testing for
  - Hematology with platelet and WBC differential

Table 10 Summary of Changes in Protocol CORT118335-877 Amendment 5

Section	Summary of Change	Revisions
Global changes	Updated version and date of the protocol.	~~Amendment 4~~**Amendment 5** ~~11 January 2022~~**09 June 2022**
Cover Page	Change in Medical Monitor	[redacted]
Synopsis	Updated synopsis to align with changes in the protocol body.	--
3.1 Overall Design	Study design updated to align with the treatment visits in Section 7 and the Schedule of Activities.	CORT118335-877 Study Design (Figure 3) updated.
5.11.1 Independent Data Monitoring Committee to Monitor Patient Safety	Updated text to align with language in the IDMC Charter.	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 and in the conduct and monitoring of randomized clinical trials. The IDMC will meet at least quarterly. Further details describing the **IDMC meeting frequency**, IDMC composition, contents of data reports, responsibilities, and decision rules will be described in the IDMC Charter.
6.4.1 Physical Examination and Vital Signs	Updated text to align with assessments performed at Treatment Visits (Section 7 and Schedule of Activities).	*Paragraph 1:* Physical examinations including a basic neurologic examination will be performed ~~at every visit during the study and at Follow-Up~~ **as indicated in the SoA (Appendix A)**.
6.4.3 Electrocardiogram	Updated text to align with assessments performed at Treatment Visits (Section 7 and Schedule of Activities).	*Paragraph 1:* Twelve-lead ECG tracings will be obtained in triplicate from all patients ~~at every visit during the study~~ **as indicated in the SoA (Appendix A)**.

Section	Summary of Change	Revisions
6.5 Efficacy Assessments	Updated text to align with assessments performed at Treatment Visits (Section 7 and Schedule of Activities).	*Paragraph 2:* Body weight will be measured ~~at every visit~~ **as indicated in the SoA (Appendix A)**. Body weight will be measured without overcoat and shoes, and with only light clothing. *Paragraph 3:* Waist circumference will be measured for all patients ~~at every visit~~ **as indicated in the SoA (Appendix A)**. 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.
7 Study Assessments and Procedures by Study Visit	Addition of study visits at Weeks 19, 21, 23 and 25 during the treatment period to increase safety monitoring of remaining patients on the study for any changes in reported AEs, concomitant medications, and to their laboratory values. Section numbers were renumbered.	The following study visits added: • **7.3.10 Week 19: Study Day 134 (±5 day)** • **7.3.12 Week 21: Study Day 148 (±5 day)** • **7.3.14 Week 23: Study Day 162 (±5 day)** • **7.3.16 Week 25: Study Day 176 (±5 day)** At all the visits added, the following assessments will be performed- • **Record any AEs** • **Record concomitant medications** • **Perform laboratory tests:** – **Chemistry panel** – **Hematology with platelet and WBC differential**
7.3 Treatment Period	Updated text to align with treatment visits and corresponding assessments.	~~At all clinic visits during the Treatment Period (except Weeks 8, 12, 16, 20, and 24), t~~**T**he following will be performed **as indicated in the SoA, (Appendix A)**: ….
~~7.3.10~~**7.3.11** Week 20: Study Day 141 (±5 day)	Added hematology with platelet and WBC differential laboratory assessments.	… • Perform laboratory test – Lipid panel – **Hematology with platelet and WBC differential**

Section	Summary of Change	Revisions
~~7.3.12~~**7.3.15** Week 24: Study Day 169 (±5 day)	Added hematology with platelet and WBC differential laboratory assessments.	… • Perform laboratory test – Lipid panel – **Hematology with platelet and WBC differential**
11.3.1 Source Documentation	Updated list of 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 **x-rays**, laboratory tests, and ECGs). All source data should be attributable, legible, contemporaneous, original, accurate, and completed. Changes to source data should be traceable **(i.e., dated and initialed)**, should not obscure the original entry, and should be explained, if necessary.
11.3.2 Case Report Forms	Updated text to account for paper or electronic CRFs.	The Investigator must generate and maintain complete, adequate, accurate, reliable, and legible records in a timely manner to enable full documentation of study conduct. All data entered into CRFs **(paper or electronic)** must be substantiated by and consistent with a source document. Discrepancies between CRFs and their respective source documents should be explained. ~~Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. All changes in eCRF data entry at the investigator site must obtain Investigator or designee's authorization.~~ **All changes in eCRF data entry at the study site will be performed by designated site personnel and will be in the clinical database audit trail. In the event paper CRFs are utilized, any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry.** **All changes in CRF data entry at the study site will be performed by designated site personnel.**
~~11.6.1~~**11.5.1** Inventory, Reconciliation, Return, and Disposition of Clinical Supplies	Updated text for clarity.	All study drug and related materials should be stored, inventoried, reconciled, and destroyed or returned according to applicable state and federal regulations**/government health authorities** and study procedures. Storage of study drug is described in Table 1.
~~11.6.2~~**11.5.2** Clinical-Supply Inventory	Updated text to align with Corcept protocol template.	Each clinical site is required to complete and maintain a detailed inventory 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 their designee must provide an explanation for any destroyed or missing study drug or study materials.**

Section	Summary of Change	Revisions
		The Investigator or their 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 their designee must retain all unused or expired study supplies until the study monitor (on-site clinical research associate) has confirmed the accountability data and Sponsor has approved return or destruction.
~~11.7~~**11.5.6** Drug Availability	Updated text to align with Corcept protocol template.	It is the responsibility of the Investigator to maintain drug accountability at the study site and ensure that a current record of study-drug disposition is maintained. **It is the responsibility of the Investigator to ensure that the study drug 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, lost, or accidentally or deliberately destroyed study product. Dispensing records will document quantities received from the Sponsor (or designee) and quantities dispensed to patients, including lot number, date dispensed, patient identifier number, patient initials, the initials of the person dispensing the drug, quantities of drug returned by the patients and disposal/return of returned study drug. ~~Prior to destruction of returned study drug, the study monitor should confirm drug accountability, if allowed by local institutional policy.~~
~~11.8~~**11.6** Post-trial Care	Updated text to align with Corcept protocol template.	~~Not applicable.~~ **There is no provision for continued access to study drug (Section 5.10).**
~~11.9~~**11.7** Protocol Noncompliance	Updated text to align with Corcept protocol template.	A protocol deviation is any noncompliance with requirements in the clinical-trial protocol, GCP, or the manual of procedures (MOP). The noncompliance may be on the part of the patient, the Investigator, or the study-site staff. As a result of deviations, corrective actions consistent with ICH E6**(R2)** may be implemented. **Prospective approval of deviations from the inclusion and exclusion criteria, known as ~~P~~p**rotocol waivers or exemptions are not permitted. Changes to the conduct of the protocol may not be made, except to address an immediate risk to the subject, unless the change has been submitted to the regulatory authorities for review and the change has been approved by the IRB. ~~Corcept~~ **Sponsor** clinical-study staff and contractors may acknowledge, but not approve, protocol deviations reported by a site that have happened or are planned to happen. Any significant protocol deviations affecting patient eligibility and/or safety or data integrity must be submitted to the IRB and regulatory authorities, as ~~required~~ **applicable, prior to implementation**. After the protocol is approved by the Sponsor and by IRBs, any change that might affect the approval of the IRBs must be documented in the form of a protocol amendment. The amended protocol must be approved by the IRB and annually, as local regulations require.

Section	Summary of Change	Revisions
11.10 Electronic Systems	Added new section on electronic systems to align with Corcept protocol template.	**All electronic systems, including clinical study sites, clinical operations, data management, biostatistics, safety, and CRO systems, etc., used to collect, manage, and store study data should be validated and in compliance with 21 CFR Part 11. The validation documentation should be made available at all times during inspection or Sponsor audits. Any modification to the validated system should be documented via a quality change control process and justified to their intended use.**
Appendix A	Updated Schedule of Activities to align with changes in the protocol.	Added assessments to align with visits added to Section 7.