Title: A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Efficacy, and Pharmacokinetics of Miricorilant in Patients with Presumed Nonalcoholic Steatohepatitis (NASH)

NCT Number: NCT03823703

Date of Original Protocol: 1 July 2020

# CLINICAL STUDY PROTOCOL CORT118335-860

| | |
|---|---|
| Title | **A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Efficacy, and Pharmacokinetics of Miricorilant in Patients with Presumed Nonalcoholic Steatohepatitis (NASH)** |
| Investigational Product | Miricorilant |
| Medical Monitor | [redacted] |
| Sponsor | Corcept Therapeutics Incorporated<br>149 Commonwealth Drive<br>Menlo Park, California 94025 US<br>(650) 327-3270 |
| Version | Amendment 2 |
| Date | 07 December 2020 |

## 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:

[redacted]

12-9-2020

Date

Chief Medical Officer
Corcept Therapeutics

## Protocol Synopsis

| **Name of Sponsor** | **Name of Active Ingredient** | **Study Number** |
|---|---|---|
| Corcept Therapeutics | Miricorilant | CORT118335-860 |

**Title of Study**

A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Efficacy, and Pharmacokinetics of Miricorilant in Patients with Presumed Nonalcoholic Steatohepatitis (NASH)

**Study Centers**

Approximately 15 sites in the US

**Phase of Development**

Phase 2a

**Study Objectives**

**Primary Efficacy**

- To assess the efficacy of both dose levels of miricorilant versus placebo in reducing liver fat content.

**Secondary Efficacy**

- To assess the efficacy of both dose levels of miricorilant combined versus placebo in reducing liver fat content.
- To assess the efficacy of miricorilant versus placebo on change in biomarkers of NASH disease activity.

**Exploratory**

- To be assessed by patient group:
  - In all patients, change in adrenocorticotropic hormone (ACTH), serum cortisol, serum aldosterone, absolute body weight, and insulin resistance.
  - In patients with diabetes, change in glycated hemoglobin A1c (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 liver fat content.
- To evaluate the exposure-response relationship between miricorilant and change in liver fat content.

**Safety**

- To assess the safety and tolerability of miricorilant versus placebo.

**Pharmacokinetic (PK)**

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

**Population**

Patients with presumed NASH.

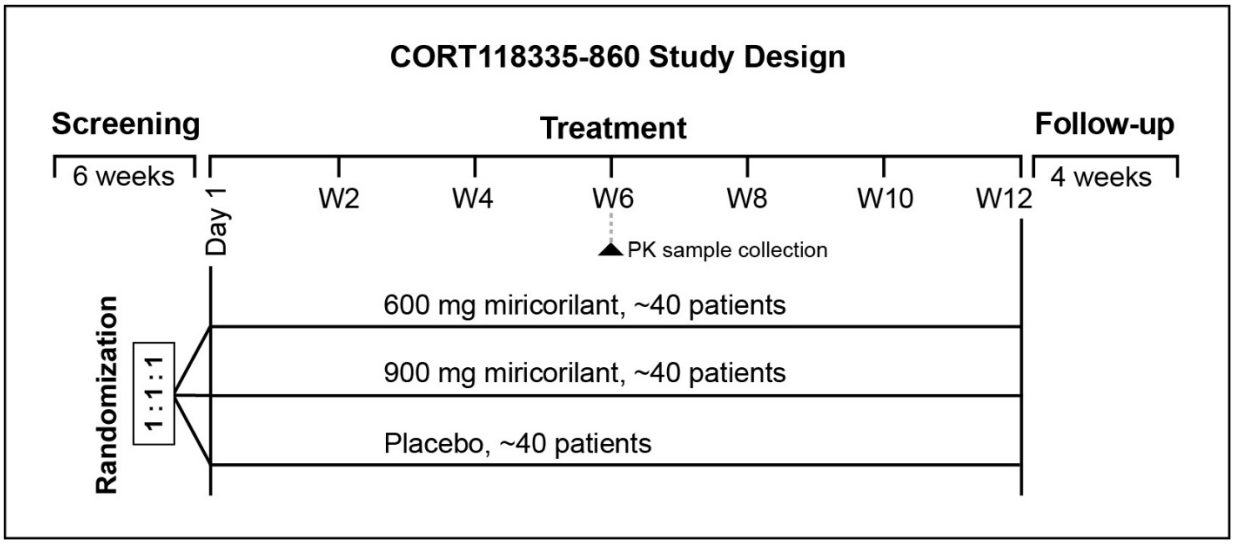
**Number of Patients Planned**

Approximately 120 patients will be enrolled in the study.

**Methodology**

This is a Phase2a, randomized, double-blind, placebo-controlled study conducted in 120 patients with presumed NASH, based on blood tests and noninvasive measures, to evaluate the safety, tolerability, PK, and preliminary efficacy of miricorilant. (Figure S1).

**Figure S1 CORT118335-860 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 12 weeks of treatment. Randomization will be stratified by the presence or absence of diabetes (see Section 3.6).

Blood samples for the measurement of miricorilant plasma concentrations will be collected at Week 6 according to the PK plan.

**Duration of Treatment and Duration of Study**

The maximum expected duration of a patient's participation is 22 weeks consisting of the following study periods:

- Screening Period: Up to 6 weeks
- Treatment Period: Day 1 (Baseline) to Week 12
- 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 ≤75 years old.
- Have a diagnosis of presumed NASH with fibrosis defined as meeting all of the following criteria:
  a. Either:

  (i) A historical liver biopsy within 1 year of Screening showing NASH, NAFLD Activity Score (NAS) ≥4, and F1 to F3 fibrosis

  OR

  (ii) The following two criteria based on non-invasive measurements:

- Aspartate aminotransferase (AST) >17 U/L for women and AST >20 U/L for men AND
- FibroScan liver stiffness measurement ≥8.5kPa and Controlled Attenuation Parameter (CAP) ≥300 dB/m in the 3 months prior to Screening or at Screening

b. MRI-PDFF with ≥10% steatosis

c. Presence of 2 or more components of metabolic syndrome: type 2 diabetes treatment or fasting blood glucose ≥126 mg/dL, BMI ≥30 kg/m$^2$, hypertension treatment or blood pressure ≥130/85, history of dyslipidemia, or waist circumference ≥102 cm (40 in) in men and ≥88 cm (35 in) in women

- Must have consistent alanine aminotransferase (ALT) and AST Baseline measurements, established by 2 samples obtained at least 4 weeks and no more than 6 months apart. At least one of the values must be derived from Screening safety labs; historical results within 6 months of Screening may be used to provide the second value for eligibility. Unless both samples are ≤1.5×the upper limit of normal (ULN), to be eligible for study entry, the difference between the first and second measurement of ALT and AST should be ≤50%. A third sample may be repeated if the variability between the first 2 values exceeds the 50% limit. If the third sample exceeds the 50% limit (compared with the first result), the patient is not eligible.
- Patients who are taking lipid-modifying therapies must be on stable doses for at least 3 months prior to Screening and unlikely to change the dose during the study (for patients taking statin medications, please see additional restrictions in exclusion criterion #15).

**Key Exclusion Criteria**

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

- Women who are pregnant, planning to become pregnant, or are lactating.
- Have a BMI <18 kg/m$^2$.
- Are currently using any medications prohibited due to the potential for drug-drug interactions (MI) with study treatments Prohibited medications (see Section 5.4.3) must be discontinued at least 5 half-lives prior to a patient receiving their first study treatment. Administration of concomitant medications (see Section 5.4) are at the discretion of the Investigator and/or the Corcept Medical Monitor.
- Have had successful weight-loss surgery prior to Screening or are planning weight-loss surgery during the study*.

  *Patients who have had Roux-en-Y gastric bypass surgery or other surgical procedures that have a fundamentally altered gastrointestinal tract may not participate regardless of success of the procedure.
- Have any elective surgery planned during the study.
- Have significant alcohol consumption, defined as more than 2 drink units per day (equivalent to 20 g of ethanol) in women and 3 drink units per day (equivalent to 30 g of ethanol) in men for ≥3 consecutive months within 1 year prior to Screening, inability to reliably quantify alcohol intake, or score a value ≥8 on the Alcohol Use Disorders Identification Test (AUDIT) questionnaire.
- Use of drugs associated with NAFLD (e.g., amiodarone, methotrexate, oral or intravenous glucocorticoids, at supraphysiological doses (prednisone equivalent ≥5 mg/day), tamoxifen, estrogens at doses greater than those used for hormone replacement or contraception, anabolic steroids, or valproic acid) for more than 4 weeks in the 2 months prior to randomization.
- Have been treated with obeticholic acid, ursodeoxycholic acid (Ursodiol® and Urso®), pioglitazone or high-dose vitamin E (>400 IU/day) within the 3 months prior to Screening imaging studies.
- Have had liver transplantation or plan to have liver transplantation during the study.

- Have type 1 diabetes.
- Have type 2 diabetes and:
  - An HbA1c ≥9.5%.
  - Have had an insulin dose adjustment >10% within 60 days prior to enrollment.
  - Have a requirement for glucagon-like peptide analogue (unless on a stable dose ≥3 months prior to Screening), a requirement for sodium/glucose cotransporter 2 (SGLT2) inhibitors (unless on a stable dose ≥3 months prior to Screening), or 3 or more oral anti-diabetic (OAD) agents (unless the OAD is stable and HbA1c <8%).
  - Have a history of severe hypoglycemia (symptomatic hypoglycemia requiring outside assistance to regain neurologic status).
- Are currently taking a statin other than stable doses of the following: lovastatin (up to 20 mg), pravastatin, pitavastatin, simvastatin (up to 10 mg), atorvastatin (up to 20 mg), or fluvastatin (up to 20 mg). A stable dose is defined as no changes in the dose in the last 3 months prior to Screening.
- Are currently on the oral antidiabetic drug nateglinide (Starlix).

  Patients currently taking the medication may participate in the study if it is 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.
- Are currently using a medication such as digoxin with an increased risk for toxicity in the event of electrolyte changes.
- Have weight loss of greater than 10% within the last 6 months prior to Screening.
- Have abnormal screening laboratories:
  a. AST >5× upper limit of normal (ULN)
  b. ALT >5× ULN
  c. Estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73 $m^2$
  d. Creatine kinase >3×ULN
- Have known or suspected cirrhosis based on the opinion of the Investigator. The list below represents possible signs of suspected cirrhosis:
  a. Physical exam findings:
     i. Jaundice
  b. Laboratory findings
     i. Direct bilirubin >0.3 (except for patients who have Gilbert's syndrome)
     ii. Platelet count <140,000/µL
  c. Imaging:
     i. Evidence of portal hypertension (dilated portal vein, presence of varices)
     ii. Evidence of a nodular liver with splenomegaly
  d. Endoscopy:
     i. Evidence of esophageal varices
- Have hepatic decompensation defined as the presence of any of the following:
  - Serum albumin <3.5 g/dL
  - International normalized ratio (INR) >1.3 (unless due to therapeutic anticoagulants)
  - Total bilirubin >1.3 mg/dL (except for patients who have Gilbert's syndrome)
  - History of esophageal or gastric variceal bleedings, ascites, or hepatic encephalopathy
- Have any other chronic liver disease:

- Hepatitis B as defined by presence of hepatitis B surface antigen
- Hepatitis C as defined by presence of hepatitis C virus (HCV) antibody and positive HCV RNA. Documented cured HCV infection is acceptable if >3 years from Screening visit
- History of current active autoimmune hepatitis
- History or evidence of primary biliary cholangitis
- History or evidence of primary sclerosing cholangitis
- History or evidence of Gilbert's syndrome if direct bilirubin is elevated (in addition to total bilirubin ≥2) or evidence of hemolysis contributing to elevated total bilirubin
- History or evidence of Wilson's disease
- History or evidence of alpha-1-antitrypsin deficiency
- History or evidence of hemochromatosis
- History or evidence of drug-induced liver disease, as defined on the basis of typical exposure and history
- Known bile duct obstruction
- Suspected or proven liver cancer
- Any other type of liver disease other than NASH

**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.

- 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**

Relative change from Baseline to Week 12 in liver fat content assessed by magnetic resonance imaging–proton density fat fraction (MRI-PDFF) for both dose levels of miricorilant versus placebo.

**Secondary Efficacy Endpoints**

The following endpoints will be assessed relative to Baseline:

- Change in liver fat content assessed by MRI-PDFF for both dose levels of miricorilant combined versus placebo.
- Proportion of patients achieving a relative reduction in liver fat content of ≥30% by MRI-PDFF for miricorilant versus placebo.
- Absolute change in liver fat content by MRI-PDFF for miricorilant versus placebo.
- Change in AST, ALT, and gamma-glutamyl transferase (GGT) for miricorilant versus placebo.
- Change in propeptide of type III collagen (pro-C3) for miricorilant versus placebo.
- Change in enhanced liver fibrosis (ELF) score and its components (hyaluronic acid, tissue inhibitor of metalloproteinases-1 [TIMP-1], type III procollagen [PIIINP]) for miricorilant versus placebo.

**Exploratory Endpoints**

The following endpoints will be assessed relative to Baseline:

- Proportion of patients achieving a relative reduction in liver fat content of ≥50% by MRI-PDFF for miricorilant versus placebo.

- Proportion of patients with complete resolution of fatty liver by MRI-PDFF for miricorilant versus placebo.

In all patients:

- Change in ACTH, serum cortisol, and serum aldosterone (pharmacodynamic assessments).
- Change in absolute body weight.
- Change in Homeostatic Model Assessment of Insulin Resistance (HOMA-IR).

In patients with diabetes:

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

In patients with high blood pressure:

- 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 measurements.
- 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***

Each dose of miricorilant will be compared with placebo on the key efficacy endpoint: the relative change from Baseline in LFC assessed by MRI-PDFF, where relative change is defined as 100 × (LFC at Week 12–LFC at Baseline)/LFC at Baseline. The primary analysis will use a nonparametric, rank analysis of covariance (ANCOVA) that incorporates Baseline LFC as a covariate; treatment group (2 dose levels of miricorilant and placebo) and diabetes status (stratification factor) as factors; and rank relative change in LFC as the response variable. P-values for the comparisons of each miricorilant dose group to placebo will be derived from linear contrasts. The Hodges-Lehmann method will be used to estimate the median differences between groups and their 95% confidence intervals (CIs). P-values from the comparisons will not be adjusted for multiplicity.

A sensitivity analysis of the primary endpoints will be performed that requires fewer assumptions than the primary analysis. The sensitivity analysis will employ 2 Wilcoxon rank-sum tests to compare each of the miricorilant dose groups to placebo; that is, one test will compare 600 mg miricorilant to placebo and another will compare 900 mg miricorilant to placebo.

The relative change in LFC in each treatment group will be summarized by the median and 25$^{th}$ and 75$^{th}$ percentiles. The primary analysis will be performed on the Efficacy Evaluable (EE) population, which includes all patients who receive at least 1 dose of study drug and remain in the trial for at least 6 weeks.

***Analysis of the Secondary Efficacy Endpoints***

The secondary efficacy endpoints will be analyzed using the EE Population unless otherwise specified.

A rank ANCOVA similar to the primary analysis will be used to test for evidence of a dose-response among the 2 miricorilant dose levels. Like the primary analysis, the model will include Baseline LFC as a covariate, diabetes status as a factor, and rank relative change in LFC as the response variable. But

in contrast to the primary analysis, the dose-response model will not include the placebo group; that is, the treatment factor will include only the 2 dose levels of miricorilant. The two miricorilant dose groups will be compared to each other using linear contrasts. The Hodges-Lehmann method will be used to estimate the median difference between the dose levels and its 95% CI. A significant difference between groups will be taken as evidence of a dose-response relationship. Dose-response will also be assessed graphically using boxplots of the relative change in MRI-PDFF for each treatment group.

A set of 3 Cochran-Mantel-Haenszel (CMH) tests–one for each pairwise comparison of treatment groups – will be used to evaluate the secondary endpoint of the proportion of patients achieving a relative reduction in LFC of ≥30% by Week 12. Each CMH test will be stratified by diabetes status. A p-value will be reported for each test along with an estimate of the common relative risk of achieving a ≥30% reduction in LFC. Each relative risk estimate will be accompanied by a 95% CI. The percentage of patients in each group who achieve a ≥30% reduction in LFC will be presented along with a 95% CI.

The absolute change in LFC from Baseline to Week 12 will be assessed using a parametric ANCOVA model with Baseline LFC as a covariate, diabetes status and treatment group as factors, and the arithmetic difference between LFC at Week 12 and Baseline as the response variable. Linear contrasts from the model will compare each of the 2 dose levels of miricorilant to placebo. A similar ANCOVA that excludes the placebo group will be used to assess dose-response in absolute LFC change. A linear contrast from the model will compare the 2 doses of miricorilant to each other. The least squares means and associated confidence intervals derived from each model will be reported.

Other continuous secondary endpoints that are measured more than once during treatment will be analyzed using linear mixed models for repeated measures (MMRM). These endpoints include the change in AST, ALT, GGT, pro-C3, and ELF score and each of its components (TIMP-1, PIIIN, and hyalauronic acid). Restricted maximum likelihood (REML) estimation will be used. Each MMRM model will include Baseline LFC as a covariate; treatment, diabetes status, visit, and treatment by visit interaction as fixed effects; and patient within treatment group as a random effect. Comparisons of each miricorilant group to placebo and to each other will be based on the estimates from the model.

***Analyses of Exploratory Endpoints***

The proportion of subjects achieving a relative reduction in LFC of ≥50%, and the proportion with a complete resolution, will be analyzed using CMH tests analogous to those used to evaluate the secondary endpoint of the proportion of patients achieving a relative reduction of ≥30%.

Analyses of continuous endpoints, such as the change in ACTH, serum cortisol, and serum aldosterone from Baseline to Week 12, will be analyzed using parametric ANCOVA models with Baseline LFC as a covariate, diabetes status and treatment group as factors, and the arithmetic difference between the endpoint at Week 12 and Baseline as the response variable. Changes in HbA1c and fasting blood glucose within patients with diabetes will employ pairwise Wilcoxon rank-sum tests to compare treatment groups. A similar strategy will be used to compare groups on the change from Baseline in blood pressure among patients with high blood pressure.

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

***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, 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 approximately 40 patients/group or approximately 120 subjects randomized 1:1:1 across 2 miricorilant treatment groups and one placebo group. The sample size calculation assumes that the SD for change in LFC due to treatment will be comparable to that observed in Patel et al. 2016, where an SD of 33% was reported, and in Harrison et al. 2019, where the SD was not reported but can be estimated from confidence intervals to be about 28%. A slightly more conservative estimate of 35% is assumed for the calculation here. Assuming that placebo patients experience a reduction in LFC of 10%, 34 patients per group affords 80% power to detect a significant difference at the $\alpha$=0.05 level between either miricorilant dose group and placebo as long as the miricorilant group achieves a 35% or greater reduction in LFC. Assuming that up to 10% of patients may drop out prior to the Week 12 MRI-PDFF assessment, the required sample size increases to 38 patients per group or 114 total patients. The sample size has been rounded up to 40 patients per group, or 120 total patients, for convenience. The sample size estimate has not been adjusted for multiple comparisons.

## Contents

## List of Tables



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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 |
| ANCOVA | analysis of covariance |
| AST | aspartate aminotransferase |
| AUC | area under the concentration-time curve |
| AUDIT | Alcohol Use Disorders Identification Test |
| BCRP | breast cancer resistance protein |
| BMI | body mass index |
| CFR | Code of Federal Regulations |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CYP | cytochrome P450 |
| DILI | drug-induced liver injury |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| EE | Efficacy Evaluable |
| ELF | enhanced liver fibrosis |
| FSH | follicle-stimulating hormone |
| GC | glucocorticoid |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| GMP | Good Manufacturing Practice |
| GR | glucocorticoid receptor |
| HbA1c | glycated hemoglobin |
| HCV | hepatitis C virus |
| hERG | human ether-á-go-go-related gene |
| HME | hot melt extrudate |
| HOMA-IR | Homeostatic model assessment of insulin resistance |
| IB | Investigator's Brochure |
| ICF | informed consent form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) |

| Abbreviation | Definition |
|---|---|
| IDMC | Independent Data Monitoring Committee |
| INR | international normalized ratio |
| IRB | Institutional Review Board |
| IV | intravenous |
| IWRS | interactive web response system |
| $K_i$ | inhibition constant |
| LFC | liver fat content |
| MAD | multiple-ascending dose |
| MMRM | mixed models for repeated measures |
| MR | mineralocorticoid receptor |
| MRI | magnetic resonance imaging |
| MRI-PDFF | magnetic resonance imaging-proton density fat fraction |
| NAFLD | nonalcoholic fatty liver disease |
| NASH | nonalcoholic steatohepatitis |
| NCI | National Cancer Institute |
| NOAEL | no-observed-adverse-effect level |
| PIIINP | type III procollagen |
| PK | pharmacokinetic(s) |
| pro-C3 | propeptide of type III collagen |
| QTcF | QT interval corrected for heart rate using Fridericia's equation: $QTcF=QT/(RR^{1/3})$ |
| REML | restricted maximum likelihood |
| RSI | Reference Safety Information |
| SAD | single-ascending dose |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SD | standard deviation |
| SDD | spray-dried dispersion |
| SGLT2 | sodium/glucose cotransporter 2 |
| SoA | schedule of activities |
| TAT | tyrosine aminotransferase |
| TEAE | treatment-emergent adverse event |
| TIMP-1 | tissue inhibitor of metalloproteinases-1 |
| UGT1A1 | uridine diphosphate glucuronosyltransferase 1A1 |
| ULN | upper limit of normal |

# 1 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

## 1.1 Therapeutic Area

Nonalcoholic fatty liver disease (NAFLD) encompasses a range of conditions characterized by an increased amount of fat in the liver. In the early stages of NAFLD, the increased deposition of fat (steatosis) in the liver is believed to have a benign prognosis. However, NAFLD can develop into nonalcoholic steatohepatitis (NASH), which is characterized by histological evidence of inflammation, hepatocyte ballooning, and fibrosis. NASH is a progressive liver disorder that can lead to cirrhosis, liver failure, and predispose patients to liver cancer (Liu et al. 2016, Machado and Diehl 2016, Woods et al. 2015). Though NASH is currently the third most common cause of cirrhosis, it is anticipated to become the leading cause of cirrhosis (Konerman et al. 2018). Currently, the only current cure for cirrhosis is liver transplantation (Konerman et al. 2018). Although the exact pathogenesis of NASH is poorly understood, most patients with NASH possess one or more elements of metabolic syndrome (obesity, type 2 diabetes, dyslipidemia) (Hazlehurst et al. 2016, Asrih and Jornayvaz 2015). Treatment of NAFLD and NASH is primarily focused on lifestyle modification and the management of associated comorbidities. Treatments such as vitamin E and pioglitazone have limited efficacy and do not improve fibrosis (Sanyal et al. 2010). Although several experimental treatments are under investigation, there is currently no approved therapy for treatment of NASH (Konerman et al. 2018).

### 1.1.1 Background

Both the glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) have been implicated in the development and progression of NAFLD, and antagonists of each receptor have provided beneficial effects in rodent models of NAFLD and NASH.

Glucocorticoids (GCs), which are involved in the regulation of energy homeostasis (carbohydrate and lipid metabolism), and increased GC levels, have been implicated in the pathogenesis of obesity, hyperglycemia, and NAFLD. Elevation of GCs results in increased adipose tissue lipolysis, which causes enhanced release of non-esterified fatty acids into the circulation. These non-esterified fatty acids are taken up by the liver, leading to increased triglyceride synthesis and hepatic steatosis. GCs also increase the de novo synthesis of triglycerides by modulation the expression of genes that convert carbohydrates into fatty acids (Patel et al. 2014).

Mineralocorticoids (MCs) are a class of corticosteroids, with the primary MC being aldosterone (Gomez-Sanchez E and Gomez-Sanchez CE 2014). The MR, like the GR, is a ligand-activated transcription factor and a member of the nuclear receptor superfamily. The MR is unique among the steroid receptors in having 2 physiological ligands: aldosterone and cortisol (corticosterone in rodents), which bind the receptor with equal affinity (Fuller 2015). Recently, MR was found to be widely expressed and has been implicated in pro-inflammatory and pro-fibrotic outcomes in multiple organ classes, and in the pathogenesis of diseases such as hypertension and diabetic retinopathy (Cole and Young 2017). The full range of genes regulated by MR has not yet been elucidated, although several MR-regulated genes have been identified (Fuller 2015). These include a number of inflammatory chemokines and cytokines, cyclooxygenase-2 (COX-2), osteopontin, transforming growth factor beta (TGF-β), and type III collagens (Lieber et al. 2013).

### Animal Studies Elucidating the Role of GR and MR in NAFLD and NASH

Animal studies have contributed to the understanding of the role of GCs in the pathogenesis of NAFLD. For example, rodents on a high fat diet and chronically elevated corticosterone had a dramatic exacerbation in the development of NAFLD (D'souza et al. 2012). Increased intrahepatic lipid synthesis and reduced lipid utilization both contribute to this effect (Wang et al. 2012). Injection of the synthetic GR agonist dexamethasone in mice increases the expression of hepatic diacylglycerol acyltransferase (the enzyme that catalyzes the final step of hepatic triacylglycerol synthesis) and decreases the expression of triacylglycerol hydrolase (the lipase that hydrolyses intracellular triacylglycerol) leading to increased hepatic triacyl glyceride (Dolinsky et al. 2004).

The role of GR modulation has been demonstrated in several ways. Targeted RNA interference of the GR in the livers of diabetic mice resulted in a pronounced decrease in hepatic triglyceride concentrations in these mice (Lemke et al. 2008). Administration of the GR antagonist mifepristone to mice fed a high fat diet reduced liver injury and resulted in improved insulin sensitivity and increased plasma adiponectin concentrations (Hashimoto et al. 2013).

Aldosterone has also been implicated in NASH. The administration of the MR antagonist spironolactone in a mouse model of diet induced diabetes improved hepatic steatosis by reducing hepatic inflammation and insulin resistance (Wada et al. 2010). Spironolactone was also effective in a rat model of liver fibrosis (Fujisawa et al. 2006). The more selective MR antagonist eplerenone also attenuated the progression of liver fibrosis in a rat model of NASH (Noguchi et al. 2010), and ameliorated steatosis and hepatic fibrosis in a mouse model of NASH (Pizarro et al. 2015).

### Data in Humans Supporting Role of GR and MR in NAFLD and NASH

Patients with primary aldosteronism, which is caused by excessive production of aldosterone by the adrenal gland, have greater insulin resistance and more frequent NAFLD than normal controls. NAFLD prevalence has been reported to be 58% in patients with primary aldosteronism who are not diabetic or obese, compared with a prevalence of 20% in normal controls (Fallo et al. 2010).

There is also evidence that elevated GCs, either endogenous or exogenous, are associated with NAFLD in humans, although the available data are somewhat inconsistent (Papanastasiou et al. 2017). The GC-driven hepatic steatosis in NAFLD may provide a background for advancement to NASH in patients predisposed to lipotoxicity (Marra and Lotersztajn 2013). Additionally, GC driven insulin resistance may hasten the advancement of simple steatosis to NASH. Patients with NAFLD and diabetes have notably higher prevalence of NASH than patients with NAFLD but no diabetes (Friedman et al. 2018).

## 1.1.2 Therapeutic Hypothesis

Miricorilant is a mixed agonist/antagonist of the GR and an antagonist of the MR and is being developed for the treatment of NASH. The therapeutic hypothesis is that the combination of GR and MR modulation will provide benefit in patients suffering from NASH. The ability of miricorilant to prevent weight gain and fat deposition, and reduce lipid accumulation in the livers of mice fed a high-fat diet has recently been reported (Mammi et al. 2016). Moreover,

Koorneef et al. have reported that miricorilant is able to reverse and prevent high-fat-diet–induced lipid accumulation in the liver of mice (Koorneef et al. 2018) by increasing hepatic triglyceride secretion. [redacted]

## 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 presumed NASH. The goal of this study is to evaluate the safety, tolerability, pharmacokinetics (PK), and preliminary efficacy of miricorilant in patients with presumed NASH based on blood tests and noninvasive imaging measures.

Detailed information about miricorilant is provided in the current Investigator's Brochure (IB) for miricorilant.

### 1.2.1 Nonclinical Summary

#### 1.2.1.1 Pharmacology Related to Mode of Action

[redacted]

#### 1.2.1.2 Absorption, Distribution, Metabolism, and Elimination

[redacted]

[redacted]

### 1.2.1.3 Safety Pharmacology and Toxicology

[redacted]

## 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 antipsychotic-induced weight gain (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.

[redacted]

### 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 body mass index (BMI) in the range of 18.0 to 30.0 kg/m$^2$. In Part 1, 6 subjects received a single oral dose of 900 mg miricorilant in suspension followed by a microdose (100 µg) of [$^{14}$C]-miricorilant containing a microtracer amount of $^{14}$C given as an intravenous (IV) infusion. In Part 2, 6 subjects received a single oral dose of 150 mg [$^{14}$C]-miricorilant oral solution in

[redacted]

[redacted]

### 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.

[redacted]

### 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 2a study (CORT118335-860).

### 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 reverse recent AIWG caused by olanzapine, risperidone, or quetiapine in obese patients (BMI ≥30 kg/m$^2$) with schizophrenia; patients who have been on antipsychotic medication for one year or less and have demonstrated weight gain of ≥5% within 6 months of starting the medication are eligible. In this multi-center study, approximately 100 patients with schizophrenia 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.

[redacted]

## 1.4 Rationale for Study Design and Dose Regimen

### 1.4.1 Design Considerations

The proposed study examines the safety, efficacy, and PK of miricorilant, a mixed agonist/antagonist of the GR and an antagonist of the MR, in patients with presumed NASH based on blood tests and noninvasive measures. A role for the GR and MR in NAFLD and NASH has been suggested (see Section 1.1), and antagonists of each receptor have shown benefit in rodent models of both NAFLD and NASH.

This Phase 2a proof of concept study is designed to compare 2 doses of miricorilant (600 mg and 900 mg) to placebo and determine whether once daily dosing of miricorilant for 12 weeks results in reduction in liver fat content in patients with presumed NASH. This study will be conducted at approximately 15 sites in the US and will randomize approximately 120 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 6 weeks of Screening, 12 weeks of Treatment, and 4 weeks of Follow-up. The efficacy of miricorilant versus placebo in reducing liver fat content will be assessed. Routine assessments of safety, PK, and tolerability using AE monitoring, measurement of vital signs, 12-lead ECG recordings, physical examination, and clinical laboratory safety tests will be performed.

### 1.4.2 Rationale for Dose Selection and Regimen

Miricorilant is also being developed for the reversal of antipsychotic weight gain, which is the subject of separate investigational new drug application in the US. [redacted]

[redacted] A starting dose regimen of 600 mg once daily has been chosen for this study in NASH as it 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 examine the dose/exposure response relationship and to help establish an effective and well-tolerated dose in these patients. [redacted]

## 1.5 Benefits and Risks

Liver steatosis is thought to precede the development of NASH. Miricorilant has shown efficacy in mouse models of NASH, improving steatosis, as well as decrease cellular death and fibrosis. Imaging reversal of steatosis by at least 30% is associated with histological improvements of NASH on liver biopsy (Patel et al. 2016). Miricorilant is expected to provide benefit in patients with presumed NASH by reducing liver fat.

The risk of clinically significant safety concerns is considered low. However, potential adverse effects of miricorilant may include signs and symptoms consistent with excessive GR antagonism (e.g., weakness, tiredness, dizziness, orthostatic hypotension, hypoglycemia, dehydration, excessive weight loss, nausea, vomiting, diarrhea, and muscle aches), and excessive MR antagonism (e.g., hyperkalemia and hypotension).

Patients will be closely monitored during the study. Standard safety tests such as orthostatic vital signs and chemistry panels (refer to Table 5) will be performed at scheduled visits as outlined in the Schedule of Assessments (SoA) (Appendix A).

The effects of 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 5.3.3.

# 2 OBJECTIVES

The following objectives will be analyzed in patients with presumed NASH:

## 2.1 Primary Efficacy Objective

- To assess the efficacy of both dose levels of miricorilant versus placebo in reducing liver fat content.

## 2.2 Secondary Efficacy Objectives

- To assess the efficacy of both dose levels of miricorilant combined versus placebo in reducing liver fat content.
- To assess the efficacy of miricorilant versus placebo on change in biomarkers of NASH disease activity.

## 2.3 Exploratory Objectives

- To be assessed by patient group:
  - In all patients, change in adrenocorticotropic hormone (ACTH), serum cortisol, serum aldosterone, absolute body weight, and insulin resistance.
  - 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 liver fat content.
- To evaluate the exposure-response relationship between miricorilant and change in liver fat content.

## 2.4 Safety Objectives

- To assess the safety and tolerability of miricorilant versus placebo.

## 2.5 Pharmacokinetic Objective

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

# 3 STUDY DESIGN

## 3.1 Overall Design

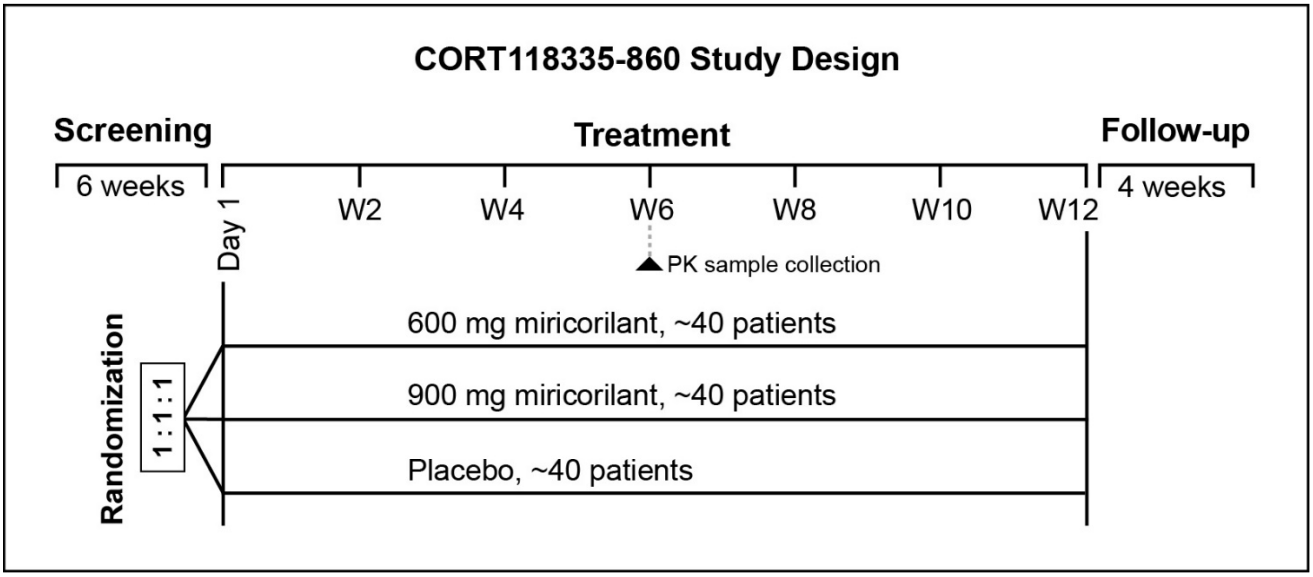
This is a Phase 2a, randomized, double-blind, placebo-controlled study conducted in 120 patients with presumed NASH, based on blood tests and noninvasive measures, to evaluate the safety, tolerability, PK, and preliminary efficacy of miricorilant.

The study consists of the following study periods:

- Screening Period: Up to 6 weeks
- Treatment Period: Day 1 (Baseline) to Week 12
- Follow-Up Period: 4 weeks after last dose of study drug

Approximately 120 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 12 weeks of treatment (Figure 1). Randomization will be stratified by the presence or absence of diabetes (see Section 3.6). See Section 9.4 for details regarding sample size calculation.

**Figure 1 CORT118335-860 Study Design**




Abbreviations: PK, pharmacokinetics; W, week.

Blood samples for the measurement of miricorilant plasma concentrations will be collected at the Week 6 visit according to the PK plan.

## 3.2 Study Endpoints

### 3.2.1 Primary Efficacy Endpoint

Relative change from Baseline to Week 12 in liver fat content assessed by magnetic resonance imaging-proton density fat fraction (MRI-PDFF) for both dose levels of miricorilant versus placebo.

### 3.2.2 Secondary Efficacy Endpoints

The following endpoints will be assessed relative to Baseline:

- Change in liver fat content assessed by MRI-PDFF for both dose levels of miricorilant combined versus placebo.
- Proportion of patients achieving a relative reduction in liver fat content of ≥30% by MRI- PDFF for miricorilant versus placebo.
- Absolute change in liver fat content by MRI-PDFF for miricorilant versus placebo.
- Change in AST, ALT, and gamma-glutamyl transferase (GGT) for miricorilant versus placebo.
- Change in propeptide of type III collagen (pro-C3) for miricorilant versus placebo.
- Change in enhanced liver fibrosis (ELF) score and its components (hyaluronic acid, tissue inhibitor of metalloproteinases-1 [TIMP-1], type III procollagen [PIIINP]) for miricorilant versus placebo.

### 3.2.3 Exploratory Endpoints

The following endpoints will be assessed relative to Baseline:

- Proportion of patients achieving a relative reduction in liver fat content of ≥50% by MRI-PDFF for miricorilant versus placebo.
- Proportion of patients with complete resolution of fatty liver by MRI-PDFF for miricorilant versus placebo.

In all patients:

- Changes in ACTH, serum cortisol, and serum aldosterone (pharmacodynamic assessments).
- Change in absolute body weight.
- Change in Homeostatic Model Assessment of Insulin Resistance (HOMA-IR).

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 6 for PK variables to be analyzed).

## 3.3 Number of Patients and Study Participation

### 3.3.1 Number of Patients

Approximately 120 patients are planned to enroll in the study (~40 per study arm).

### 3.3.2 Duration of Patient Participation

The maximum expected duration of a patient's participation is 22 weeks (6 weeks of Screening, 12 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 12 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 treatment, which may be the end of the Treatment Period if the patient completed all treatments or may be earlier if the patient discontinued study treatment before the designated stopping point.

### 3.4.4 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.

### 3.6 Diagnosis of Diabetes

Patients in the study will be stratified by diabetes. Criteria for the diagnosis of diabetes (ADA 2018) are as follows:

1. Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours.
2. 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during oral glucose tolerance test. The test should be performed as described by the World Health Organization (WHO 2006), using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.
3. HbA1c ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay.
4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).*

*In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

# 4 STUDY POPULATION

The following eligibility criteria are designed to select patients with presumed NASH based on blood tests and noninvasive measures. 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 ≤75 years old.
3. Have a diagnosis of presumed NASH with fibrosis defined as meeting all of the following criteria:
   a. Either:
      (i) A historical liver biopsy within 1 year of Screening showing NASH, NAFLD Activity Score (NAS) ≥4, and F1 to F3 fibrosis
      OR
      (ii) The following two criteria based on non-invasive measurements:
      - AST >17 U/L for women and AST >20 U/L for men AND
      - FibroScan liver stiffness measurement ≥8.5kPa and Controlled Attenuation Parameter (CAP) ≥300 dB/m in the 3 months prior to Screening or at Screening

   b. MRI-PDFF with ≥10% steatosis
   c. Presence of 2 or more components of metabolic syndrome: type 2 diabetes treatment or fasting blood glucose ≥126 mg/dL, BMI ≥30 kg/m$^2$, hypertension treatment or blood pressure ≥130/85, history of dyslipidemia, or waist circumference ≥102 cm (40 in) in men and ≥88 cm (35 in) in women
4. Must have consistent ALT and AST Baseline measurements, established by 2 samples obtained at least 4 weeks and no more than 6 months apart. At least one of the values must be derived from Screening safety labs; historical results within 6 months of Screening may be used to provide the second value for eligibility. Unless both samples are ≤1.5×the upper limit of normal (ULN), to be eligible for study entry, the difference between the first and second measurement of ALT and AST should be ≤50%. A third sample may be repeated if the variability between the first 2 values exceeds the 50% limit. If the third sample exceeds the 50% limit (compared with the first result), the patient is not eligible.
5. Patients who are taking lipid-modifying therapies must be on stable doses for at least 3 months prior to Screening and unlikely to change the dose during the study (for patients taking statin medications, please see additional restrictions in exclusion criterion #15).
6. 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 both male patients and female patients of childbearing potential; (see Section 4.6.4 and 4.6.5 for details).

## 4.2 Exclusion Criteria

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

1. Have participated in another clinical trial within the last year where patient received active treatment for NASH.
2. Have participated in a clinical trial for any other indication within the last 3 months or 5 half-lives of the treatment, whichever is longer.
3. Have participated in another Corcept study with miricorilant.
4. Women who are pregnant, planning to become pregnant, or are lactating.
5. Have a BMI <18 kg/m$^2$.
6. Are currently using any medications prohibited due to the potential for drug-drug interactions (DDI) with study treatments Prohibited medications (see Section 5.4.3) must be discontinued at least 5 half-lives prior to a patient receiving their first study treatment. Administration of concomitant medications (see Section 5.4) are at the discretion of the Investigator and/or the Corcept Medical Monitor.
7. Have had successful weight-loss surgery prior to Screening or are planning weight-loss surgery during the study*.

   *Patients who have had Roux-en-Y gastric bypass surgery or other surgical procedures that have a fundamentally altered gastrointestinal tract may not participate regardless of success of the procedure.

8. Have any elective surgery planned during the study.
9. Have significant alcohol consumption, defined as more than 2 drink units per day (equivalent to 20 g of ethanol) in women and 3 drink units per day (equivalent to 30 g of ethanol) in men for ≥3 consecutive months within 1 year prior to Screening, inability to reliably quantify alcohol intake, or score a value ≥8 on the Alcohol Use Disorders Identification Test (AUDIT) questionnaire.
10. Use of drugs associated with NAFLD (e.g., amiodarone, methotrexate, oral or intravenous GCs, at supraphysiological doses (prednisone equivalent ≥5 mg/day), tamoxifen, estrogens at doses greater than those used for hormone replacement or contraception, anabolic steroids, or valproic acid) for more than 4 weeks in the 2 months prior to randomization.
11. Have been treated with obeticholic acid, ursodeoxycholic acid (Ursodiol® and Urso®), pioglitazone or high-dose vitamin E (>400 IU/day) within the 3 months prior to Screening imaging studies.
12. Have had liver transplantation or plan to have liver transplantation during the study.
13. Have type 1 diabetes.
14. Have type 2 diabetes and:
    a. An HbA1c ≥9.5%
    b. Have had an insulin dose adjustment >10% within 60 days prior to enrollment
    c. Have a requirement for glucagon-like peptide analogue (unless on a stable dose ≥3 months prior to Screening), a requirement for sodium/glucose cotransporter 2 (SGLT2) inhibitors (unless on a stable dose ≥3 months prior to Screening), or 3 or more oral anti-diabetic (OAD) agents (unless the OAD is stable and HbA1c <8%)

d. Have a history of severe hypoglycemia (symptomatic hypoglycemia requiring outside assistance to regain neurologic status)

15. Are currently taking a statin other than stable doses of the following: lovastatin (up to 20 mg), pravastatin, pitavastatin, simvastatin (up to 10 mg), atorvastatin (up to 20 mg), or fluvastatin (up to 20 mg). A stable dose is defined as no changes in the dose in the last 3 months prior to Screening.
16. Are currently on the oral antidiabetic drug nateglinide (Starlix).

    Patients currently taking the medication may participate in the study if it is 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.

17. Are currently using a medication such as digoxin with an increased risk for toxicity in the event of electrolyte changes.
18. Have weight loss of greater than 10% within the last 6 months prior to Screening.
19. Have abnormal screening laboratories:
    a. AST >5× upper limit of normal (ULN)
    b. ALT >5× ULN
    c. Estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73 $m^2$
    d. Creatine kinase >3×ULN
20. Have known or suspected cirrhosis based on the opinion of the Investigator. The list below represents possible signs of suspected cirrhosis:
    a. Physical exam findings:
        i. Jaundice
    b. Laboratory findings
        i. Direct bilirubin >0.3 (except for patients who have Gilbert's syndrome; see exclusion criterion #21f)
        ii. Platelet count <140,000/µL
    c. Imaging:
        i. Evidence of portal hypertension (dilated portal vein, presence of varices)
        ii. Evidence of a nodular liver with splenomegaly
    d. Endoscopy:
        i. Evidence of esophageal varices
21. Have hepatic decompensation defined as the presence of any of the following:
    a. Serum albumin <3.5 g/dL
    b. International normalized ratio (INR) >1.3 (unless due to therapeutic anticoagulants)
    c. Total bilirubin >1.3 mg/dL (except for patients who have Gilbert's syndrome; see exclusion criterion #21f)
    d. History of esophageal or gastric variceal bleedings, ascites, or hepatic encephalopathy
22. Have any other chronic liver disease:
    a. Hepatitis B as defined by presence of hepatitis B surface antigen
    b. Hepatitis C as defined by presence of hepatitis C virus (HCV) antibody and positive HCV RNA. Documented cured HCV infection is acceptable if >3 years from Screening visit
    c. History of current active autoimmune hepatitis

d. History or evidence of primary biliary cholangitis
e. History or evidence of primary sclerosing cholangitis
f. History or evidence of Gilbert's syndrome if direct bilirubin is elevated (in addition to total bilirubin ≥2) or evidence of hemolysis contributing to elevated total bilirubin
g. History or evidence of Wilson's disease
h. History or evidence of alpha-1-antitrypsin deficiency
i. History or evidence of hemochromatosis
j. History or evidence of drug-induced liver disease, as defined on the basis of typical exposure and history
k. Known bile duct obstruction
l. Suspected or proven liver cancer
m. Any other type of liver disease other than NASH

23. Have a history of biliary diversion.
24. Are seropositive for human immunodeficiency virus.
25. Have a history of cancer within the last 3 years (in situ carcinomas, cutaneous basal cell or squamous cell cancer resolved by excision are not excluded).
26. Have contraindications to magnetic resonance imaging (MRI).
27. New York Heart Association class III or IV heart failure, or known left ventricular ejection fraction <30%.
28. Uncontrolled hypertension (either treated or untreated) defined as systolic blood pressure >160 mm Hg or a diastolic blood pressure >100 mm Hg at Screening.
29. Uncontrolled cardiac arrhythmia, including confirmed QT interval corrected using Fridericia's formula (QTcF) >450 msec for males and >470 msec for females at the Screening ECG assessment.
30. Myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass graft, or stroke within 3 months prior to Screening.
31. Active substance abuse, including inhaled or injected drugs, within 1 year prior to Screening.
32. Have any clinical condition or significant concurrent disease judged by the Investigator to complicate the evaluation of the study treatment.
33. Are a family member of one of the Sponsor's employees, the Investigator, or the site staff.
34. Are directly working on the study or are a contractor directly involved in the conduct of the trial.
35. 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.

Subjects who have an exclusionary laboratory result on initial screening tests may have that assessment repeated in consultation with Corcept Medical Monitor, once within the 6-week Screening period if the Investigator believes the result was spurious or otherwise confounded. The repeat assessment must meet eligibility requirement before the subject proceeds with the Screening MRI assessment.

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 study treatment while remaining on study; that is, the patient may wish to stop treatment early but may agree to continue with study visits and/or assessments.

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

### 4.4.1 Early Patient Discontinuation 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 study drug, that patient will complete an Early Termination (ET) visit at the time of the last dose of the study drug, or soon thereafter. The Follow-Up visit will be conducted 28±5 days after the last dose of the study drug. Investigators should encourage these patients to continue with all study visits and/or assessments per the patient's original study schedule through Week 12 (end-of-treatment). If the Follow-Up visit coincides with any other study visit, the assessments performed at these visits will be combined. If a patient is unable to continue with all study visits, they will be encouraged to complete the end-of treatment Week 12 visit at the very least, in addition to the ET and Follow-Up visits. Patients who complete at least 6 weeks of treatment and subsequently discontinue will be eligible for evaluation of liver fat content by MRI-PDFF. 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 5.3.

### 4.4.2 Early Patient Withdrawal from Study

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

- Withdrawal of consent.

- Noncompliance, including refusal of the study treatment and/or failure to adhere to the study requirements, as specified in protocol.
- 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 the Sponsor.

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 5.4)

### 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 consumption).

### 4.6.3 Activity

Patients should engage in physical activity 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.
- Women 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.

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 are not acceptable methods of contraception.

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 to not donate sperm during the study and for at least 28 days after the last dose of study drug.

# 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 |
|---|---|---|
| [redacted] | [redacted] | [redacted] |
| 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:<br>• In a secure location<br>• At 20°C–25°C (68°F–77°F), excursions permitted to 15°C–30°C (59°F–86°F)<br>• Out of sight and reach of children | Store as follows:<br>• In a secure location<br>• At 20°C–25°C (68°F–77°F), excursions permitted to 15°C–30°C (59°F–86°F)<br>• Out of sight and reach of children |

Procedures for inventory, reconciliation, and destruction or return of study tablets are provided in Section 11.6.

### 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.

For the week 6 visit, patients will be instructed to not take their daily study drug prior to the visit, but to bring their study drug to the site with them so that the study drug can be administered at the site.

## 5.2 Non-Investigational Medicinal Agent

Not applicable.

## 5.3 Dose Modification

### 5.3.1 Dose Reduction

No dose modification will be allowed.

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

Study treatment should be temporarily interrupted if deemed medically necessary by the Investigator. On interrupting the study treatment, the Investigator should notify the Corcept Medical Monitor. Before restarting study treatment, the Investigator must obtain approval from the Corcept Medical Monitor. If the event that necessitated treatment interruption recurs after study treatment is restarted, the patient should be permanently discontinued from study treatment. In addition, patients will be permanently discontinued from study treatment if they experience any of the criteria listed for stopping treatment in Table 2.

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

Based on the mechanism of action of miricorilant, there is a theoretical risk of excessive GR antagonism and excessive MR antagonism. Thus far in clinical experience with miricorilant in healthy volunteers as well as in patients with AIWG, an increased incidence of excessive GR or MR antagonism has not been observed. 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 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. [redacted] Symptoms should continue to be monitored even after the last dose of study medication in the follow-up period; intravenous fluids and hydrocortisone should be administered as clinically appropriate to reverse excessive GR and MR antagonism.

At each study visit starting with the Baseline visit, patients will be evaluated for signs and symptoms of excessive GR or MR antagonism. For patients who experience symptoms, the actions outlined in Table 2 should be taken.

Guidelines for temporarily interrupting and restarting and for permanently discontinuing study treatment due to other safety events (hyperkalemia; hypotension; excessive miricorilant

exposure; suspected liver injury, and significant trauma, surgery, or medical illness) are outlined in Table 2.

For assessment of suspected liver injuries, baseline values for ALT, AST and total bilirubin will be the mean of all values obtained from Screening through Day 1. Please refer to the laboratory manual or individual subject laboratory report for gender- and age-specific references.

Elevations of ALT or AST are defined as a baseline ALT or AST <ULN that increased to >3×ULN on treatment, or a baseline ALT or AST >ULN and on-treatment >2×baseline. Elevations should be confirmed with repeat testing within 48 to 72 hours. If confirmed, and if no other cause of laboratory abnormality is immediately apparent, the Corcept Medical Monitor is to be notified. Patients with ALT or AST elevations must be placed into close observation (see Table 2).

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

| Safety Event | Criteria for Interrupting and Restarting Study Treatment and Patient Management | Criteria for Stopping Study Treatment |
|---|---|---|
| Excessive GR or MR antagonism | Criteria: signs and symptoms of excessive GR and MR antagonism (Section 1.5)<br>Management:<br>• **Immediately interrupt miricorilant treatment** for ≥5 days and start standard supportive care, including intravenous fluids as indicated.<br>• 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.<br>• If the patient has been receiving treatment with an MR antagonist, consider discontinuing it, particularly in the presence of hypotension.<br>• Restart miricorilant treatment only if the workup reveals an alternative cause for symptoms of possible excessive GR/MR antagonism and after consultation with the Corcept Medical Monitor. | A combination of the following Grade 3 or higher events:<br>fatigue, anorexia, nausea, and vomiting (associated with decreased oral intake), and abdominal pain. |
| Hypotension | Criteria: development of hypotension while on study drug.<br>Management:<br>• Confirm the diagnosis by office BP monitoring and orthostatic BP measurements.<br>• Examine patient and check potassium levels.<br>• If appropriate, advise the patient to hydrate orally with electrolyte containing hydration (e.g., Gatorade or Pedialyte). Hypotension can also be supported with intravenous hydration with isotonic fluids.<br>• Patients who have hypotension should have any antihypertensive medications and diuretic medications discontinued as appropriate.<br>• Interrupt miricorilant if SBP <100 mm Hg or if DBP <60 mm Hg or if orthostatic hypotension is present or if patient requires treatment with intravenous fluids.<br>• Restart miricorilant only if hypotension is transient and reversible and not related to study medication, and after consultation with the Corcept Medical Monitor. | Systolic BP <100 mm Hg or diastolic BP <60 mm Hg (as confirmed by office BP measurements) or orthostasis, despite the discontinuation of antihypertensive medications and intravenous and oral hydration. |

| Safety Event | Criteria for Interrupting and Restarting Study Treatment and Patient Management | Criteria for Stopping Study Treatment |
|---|---|---|
| Hyperkalemia | Criteria: development of hyperkalemia during the study.<br>Management:<br>• Verify hyperkalemia and normal renal function.<br>• Obtain ECG for evaluation of hyperkalemia.<br>• Interrupt miricorilant if hyperkalemia is severe (>6.0 mEq/L) or if renal function is impaired.<br>• As medically indicated, initiate treatment for hyperkalemia.<br>• Restart miricorilant only if the underlying cause of hyperkalemia is transient and correctable and after discussion with the Corcept Medical Monitor. | Severe (>6.0 mEq/L) hyperkalemia.<br>Confirmed ECG abnormalities including peaked T waves, shortened QT interval, ST segment depression, prolonged PR interval, flattened p wave, widened QRS, amplified R wave, or intraventricular/fascicular/bundle branch blocks.<br>Underlying renal disease. |
| Suspected liver injury | Criteria: development of suspected liver injury while on study drug<br>Management:<br>• Repeat liver biochemistries (ALT, AST, total bilirubin) within 48 to 72 hours of results.<br>• Obtain a more detailed history of symptoms and prior or concurrent disease and a history of concomitant drug use (including nonprescription medication and herbal and dietary supplement preparations).<br>• Obtain a history of exposure to environment chemical agents.<br>• Rule out other causes of liver disease as needed, if required in the opinion of the Investigator.<br>• Obtain additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).<br>• Continue to monitor the liver biochemistry at least twice weekly. Frequency can decrease to once a week or less if abnormalities stabilize or study drug has been discontinued and the patient is asymptomatic.<br>• During the period of close observation, study drug can be continued if desired at the discretion of Corcept Medical Monitor and Investigator. | For patients with elevated baseline AST, ALT, total/direct bilirubin (>ULN)<br>• If baseline value was <2×ULN, discontinue if ALT or AST increases to >5×baseline.<br>• If baseline value was ≥2×ULN but <5×ULN, discontinue if ALT or AST increases to >3×baseline.<br>• If baseline value was ≥5×ULN, discontinue if ALT or AST increases to >2×baseline.<br>• If ALT or AST increases to >2×baseline value and the increase is accompanied by a concomitant increase in total bilirubin to >2×baseline value or an increase in INR by >0.2. If a patient has Gilbert's syndrome, ≥35% of total bilirubin must also be direct bilirubin.<br>• In any patients with signs and symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%). |

| Safety Event | Criteria for Interrupting and Restarting Study Treatment and Patient Management | Criteria for Stopping Study Treatment |
|---|---|---|
| Significant trauma, surgery, or medical illness at any time during the study (through 2 weeks after last dose) | Management:<br>• As medically indicated, interrupt miricorilant treatment and provide supplemental hydrocortisone to offset the GR antagonism even in patients not experiencing signs and symptoms of excessive antagonism.<br>• After resolution of the physiological stress associated with the event and if still within the Treatment Period, resume miricorilant. | Patient does not recover from the significant trauma, surgery, or medical illness within the Treatment Period. |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; DBP, diastolic blood pressure; DILI, drug-induced liver injury; ECG, electrocardiogram; GR, glucocorticoid receptor; INR, international normalized ratio; MR, mineralocorticoid receptor; SBP, systolic blood pressure; ULN, upper limit of normal.

### 5.3.4 Pharmacokinetic Criteria for Dose Adjustment or Discontinuation

Not applicable.

## 5.4 Concomitant Medications

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

### 5.4.1 Permitted Concomitant Medications

Medications required to treat AEs, manage symptoms, concurrent diseases, and supportive care agents, such as pain medications, anti-emetics, and antidiarrheal agents, are allowed at the discretion of the Investigator and/or the Corcept Medical Monitor. Patients must be instructed to notify the investigational site about any new medications they take after the start of the study drug. All medications (other than study drugs) administered 28 days before study entry (i.e., after a patient signs the ICF) and during the study must be listed on the concomitant medications eCRF.

Permitted concomitant medications are listed in Table 3.

**Table 3 Permitted Concomitant Medications**

| Medication | Use and/or Restriction |
|---|---|
| Insulin and oral antidiabetic medication | Dose can be decreased during treatment with study drug to prevent hypoglycemia; upward titration should be avoided and may occur only after consultation with the Corcept Medical Monitor. |
| Antihypertensive medication | Dose can be decreased during the treatment with study drug to prevent hypotension or orthostatic symptoms.<br>Do not increase dose or add new antihypertensive medications without prior consultation with the Corcept Medical Monitor. |
| Lipid-modifying drug | No changes in current dose allowed from 6 weeks before Baseline through the Follow-up Visit.<br>Do not add new lipid-modifying medications without prior consultation with the Corcept Medical Monitor. |

### 5.4.2 Permitted Concomitant Therapy Requiring Caution

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

- Moderate inducers of CYP2C19.
- Strong inhibitors of CYP3A4, CYP2C8, and/or CYP2C9.
- Prescription or over-the-counter medications that are a substrate for breast cancer resistance protein (BCRP) or uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) and are not prohibited with BCRP and/or UGT1A1 inhibitors and for which an acceptable dose modification can be implemented to allow coadministration with miricorilant.
- Medications that carry a possible risk for QT prolongation.

**Table 4 Cautionary Measures for Permitted Concomitant Medications**

| Medication | Cautionary Actions |
|---|---|
| Simvastatin | Simvastatin should be dosed in the evening as per its label and separated from the morning dose of miricorilant by 12 hours. |
| Atorvastatin | Atorvastatin should be dosed in the evening and separated from the morning dose of miricorilant by 12 hours. |
| Fluvastatin | Fluvastatin should be dosed in the evening as per its label and separated from the morning dose of miricorilant by 12 hours. |
| Glyburide | Fingerstick blood glucose monitoring may need to be increased from Baseline to Week 2. |
| Losartan | Dosing should be separated from miricorilant by 12 hours.<br>Blood pressure monitoring may need to be increased from Baseline to Week 2. |

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

### 5.4.3 Prohibited Medications

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

- Other investigational therapies.
- Prescription or over-the-counter medications that are moderate and strong inhibitors of CYP2C19.
- Prescription or over-the-counter medications that are strong inducers of CYP2C19.
- Prescription or over-the-counter medications with a narrow therapeutic index that are predominantly metabolized by CYP3A4, CYP2C8, and/or CYP2C9.
- Prescription or over-the-counter medications that are a substrate for BCRP or UGT1A1 and have clinically significant in vivo drug-drug interactions with BCRP and/or UGT1A1 inhibitors and for which an acceptable dose modification is not an option.
- Digoxin or other medications with increased risk for toxicity in the event of electrolyte changes.
- Systemic corticosteroids (with exception of temporary use for treatment of excessive GR antagonism), potent (group III) topical corticosteroids, and intra-articular corticosteroid.
- The oral antidiabetic drug nateglinide (Starlix).

## 5.5 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 diabetes status to ensure that there will be an equal number of patients with diabetes in each treatment group. Before the study is initiated, the log-in information and directions for the IWRS will be provided to each site.

Study drug will be dispensed at the study visits summarized in the SoA (Appendix A).

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

## 5.6 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.

## 5.7 Dosing Diary

A dosing diary will be provided, and patients will be instructed to return all unused study drug 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 as well as the date and time of study drug administration. Time and dose administered should be documented in the clinic charts.

## 5.8 Study Drug Accountability and Treatment Adherence

Study drug adherence will be determined by review of the patient dose diary and counting returned tablets. On visit days, study drug should be taken in the clinic during the visit and after initial blood draws.

A patient who is assigned a study drug (i.e., to 600 mg miricorilant, 900 mg miricorilant or placebo, for 12 weeks of treatment) will be considered nonadherent if he or she misses >20% 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.

## 5.9 Continued Access to Study Drug

There is no provision for continued access to study drug.

## 5.10 External Data Review Committee(s)

### 5.10.1 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 3 voting members: two physicians and one statistician. The IDMC will meet at least quarterly. Further details describing the IDMC composition, contents of data reports, responsibilities, and decision rules will be described in the IDMC Charter.

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

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

The Investigator and Sponsor will conduct the study in accordance with International Council 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. The 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

Comprehensive physical examinations will be performed at Screening, Baseline, Early Termination, and Follow-up. Symptom-directed physical examinations will be performed at the other study visits. Genitourinary, rectal, and breast examinations are not required.

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 will include resting heart rate, blood pressure, respiratory rate, and body temperature. Systolic and diastolic blood pressure will be measured after patients have been at rest (seated) for at ≥3 minutes. Blood pressure will be recorded in mm Hg. Heart rate (beats per minute) will be measured 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 and Weight

Height will be measured once, at Screening.

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

BMI will be autocalculated from the electronic data capture (EDC) database at every visit.

### 6.4.3 Electrocardiogram

Twelve-lead ECG tracings will be obtained in triplicate from all patients at each visit during the study. 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 of the ICF until 28 days after the last dose of 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. Additional analyses may be performed to evaluate the effects of miricorilant (see Appendix A).

Laboratory values for an analyte that are outside of the normal range for that analyte per the applicable central or local laboratory will be identified and assessed as clinically significant or not and can be 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 5 and should be performed according to the schedule provided in the SoA (Appendix A).

**Table 5 Clinical Laboratory Variables Evaluated During the Study**

| **Hematology** | **Serum Chemistry** | **Pharmacodynamic Biomarkers** |
|---|---|---|
| Red blood cell count<br>Hemoglobin<br>Hematocrit<br>Mean corpuscular hemoglobin<br>Mean corpuscular hemoglobin volume<br>Mean corpuscular volume<br>Platelet count<br>  Mean platelet volume<br>  Red blood cell distribution width<br>White blood cell count with 5-part differential<br>  Neutrophils (percent and absolute)<br>  Lymphocytes (percent and absolute)<br>  Monocytes (percent and absolute)<br>  Eosinophils (percent and absolute)<br>  Basophils (percent and absolute) | Sodium<br>Potassium<br>Calcium<br>Chloride<br>Phosphorus<br>Magnesium<br>Serum Creatinine<br>Bilirubin (total and direct)<br>Albumin<br>Alkaline phosphatase<br>Aspartate aminotransferase<br>Alanine aminotransferase<br>Plasma glucose (fasting)<br>Serum insulin (fasting)<br>Glycated hemoglobin (HbA1c)<br>Blood urea nitrogen<br>Uric acid<br>Bicarbonate<br>Total protein<br>Gamma-glutamyl transferase (GGT)<br>Creatine kinase | Adrenocorticotropic hormone (ACTH)<br>Serum cortisol<br>Serum aldosterone<br>Propeptide of type III collagen (pro-C3)<br>Enhanced liver fibrosis (ELF) score and components (hyaluronic acid, tissue inhibitor of metalloproteinases-1 [TIMP-1], type III procollagen [PIIINP]) |
| | | **Other Biomarkers** |
| | | Glucocorticoid receptor activity |
| | | **Pharmacokinetics** |
| | | Miricorilant |
| **Lipid Panel (Fasting)** | | **Pregnancy** |
| Total cholesterol<br>Low-density lipoprotein-cholesterol<br>High-density lipoprotein-cholesterol<br>Very-low-density lipoprotein cholesterol<br>Triglycerides | **Hormones** | Serum/urine pregnancy test (for women of childbearing potential) |
| | Follicle-stimulating hormone (FSH) | |
| **Coagulation** | **Other** | |
| Prothrombin/international normalized ratio<br>Partial Thromboplastin time | Virus screen (human immune-deficiency virus, hepatitis C and B viruses) | |

Note: See the Schedule of Assessments (Appendix A) for the laboratory test schedule.

#### 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 11.5.

#### 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

All efficacy assessments will be performed at the time points specified in the SoA (Appendix A).

### 6.5.1 Magnetic Resonance Imaging-Derived Proton Density Fat Fraction

Recent data support the use of MRI-PDFF in early-phase NASH clinical trials, as a noninvasive, quantitative measure of the level of fat in the liver (Caussy et al. 2018). Changes in liver fat content greater than 30% are correlated with improvements in liver fibrosis by biopsy (Patel et al. 2016). MRI-PDFF will be performed to determine the degree of LFC reduction. Instructions for preparing for and performing the test will be provided in the study manual.

### 6.5.2 NASH Biomarkers

NASH biomarkers include AST, ALT, GGT, pro-C3, ELF score and its components (hyaluronic acid, TIMP-1, PIIINP).

Blood for measuring levels of AST, ALT, and GGT (as part of the chemistry panel) will be collected.

Small fragments of collagen, called propeptides, are released during fibrosis. Pro-C3 is the propeptide of type III collagen and detection of pro-C3 is anticipated to reflect the formation of new fibrotic tissue in the liver (Vilar-Gomez and Chalasani 2018). Blood samples for measuring pro-C3 will be collected (also see Section 6.6).

The ELF score combines 3 serum biomarkers (hyaluronic acid, TIMP-1, and PIIINP) which have been shown to correlate with the degree of liver fibrosis assessed by liver biopsy (Vilar-Gomez and Chalasani 2018). Each of these markers is measured by an immunoassay and an ELF score is generated, from which a level of fibrosis severity can be determined. Blood samples will be collected at the time points specified in the study SoA (Appendix A, see also Section 6.6).

### 6.5.3 Glycated Hemoglobin (HbA1c)

Blood samples will be collected from all patients to measure HbA1c, a glycoprotein whose concentration reflects the amount of glucose bound to hemoglobin (Bala et al. 2017). Blood samples will be collected at the time points specified in the SoA (Appendix A).

### 6.5.4 Weight

Weight will be measured at all visits and will be used in BMI calculations.

## 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 6). Pharmacokinetic 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 6 Pharmacokinetic Parameters to be Evaluated***

| | |
|---|---|
| $\lambda_z$ | apparent terminal rate constant |
| AUC | area under the concentration-time curve |
| $AUC_{last}$ | AUC values from time 0 to time of last measurable concentration |
| $AUC_{tau}$ | AUC over the dosing interval |
| 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 |
| $V_{ss}$ | 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 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, or serum) will be obtained, some for analysis during the study and others for future analysis. 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.

In the event of pharmacodynamic marker extraction failure, a replacement blood sample may be requested from the patient.

## 6.8 Other Assessments

### 6.8.1 Patient-Reported Outcomes

An alcohol consumption screen will be performed at Screening. AUDIT is a validated 10-item questionnaire developed to assess alcohol consumption, drinking behaviors, and alcohol-related problems. A score of 8 or more is considered to indicate hazardous or harmful alcohol use (Reinert and Allen 2007).

### 6.8.2 FibroScan

FibroScan is a specialized ultrasound machine that is used to measure both liver fibrosis and steatosis (Afdhal 2012). FibroScan will be performed at Screening (or scans performed 3 months

within Screening are acceptable). Instructions for preparing for and performing the test will be provided in the study manual.

## 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 ACTIVITIES BY STUDY VISIT

An SoA is provided in Appendix A.

Corcept will be promptly notified of any protocol deviations.

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

## 7.1 Screening (6 weeks; Day -42 to Day -1)

Screening will occur within 6 weeks before the first dose of the study drug. 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 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 and assessments will be performed:

- Obtain informed consent
- Record medical history
- Record prior and concomitant medications
- Record AEs
- Record demographic information
- Perform physical examination
- Record vital signs (including orthostatic vital signs)
- Perform 12-lead resting ECG (in triplicate)
- Measure height and body weight
- Measure waist circumference
- Conduct AUDIT screen
- Obtain FibroScan or verify that FibroScan has been done within 3 months of Screening
- Draw blood samples for laboratory tests
  - Chemistry panel
  - Hematology with platelet and WBC count differential
  - Lipid Panel
  - Serum pregnancy test (women of childbearing potential only)
  - FSH for females who have a medically confirmed ovarian failure or are postmenopausal
  - Prothrombin time/international normalized ratio (INR)
  - HbA1c

  - HIV screening
  - Hepatitis B (HBV) screening
  - Hepatitis C (HCV)screening
- If patient continues to be eligible following laboratory tests, perform MRI-PDFF during a separate visit.

## 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 history and review of medications
  - Perform urine pregnancy test (women of childbearing potential only); if urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test
  - Measure body weight
  - 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
- Draw blood samples for laboratory tests
  - Chemistry panel
  - Hematology with platelet and WBC count differential
  - Lipid panel
  - Serum cortisol (morning 8:00–AM ±1 hour)
  - Serum aldosterone
  - ACTH (morning 8:00–AM ±1 hour)
  - Prothrombin time/INR
  - HbA1c
  - Serum insulin
  - Plasma glucose
  - NASH biomarkers (Table 5)
- Other Biomarker Assessment
  - Glucocorticoid-receptor activity marker
- Record AEs
- Perform study randomization
- Dispense study drug; patient will take their first dose of study drug in the clinic at this visit after clinic assessments
- Provide the patient with dose diary

## 7.3 Treatment Period

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

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

- Record any AEs
- Record concomitant medications
- Perform urine pregnancy test (women of child-bearing potential); if urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test
- Perform physical examination
- Measure body weight
- Record vital signs (including orthostatic vital signs)
- Perform 12-lead resting ECG (in triplicate)
- Perform laboratory tests:
  - Chemistry panel
  - Hematology with platelet and WBC count differential
- Record unused study drug brought back by the patient
- Evaluate study treatment adherence 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)

The following procedures and assessments will be performed in addition to those listed in Section 7.3.

- Dispense study drug

### 7.3.2 Week 4: Study Day 29 (±2 days)

The following procedures and assessments will be performed in addition to those listed in Section 7.3.

- Perform laboratory tests:
  - Lipid panel
  - Serum insulin
  - Plasma glucose
- Dispense study drug

### 7.3.3 Week 6: Study Day 43 (±2 days)

The following procedures and assessments will be performed in addition to those listed in Section 7.3. For the PK analysis, all patients will be required to take their dose in the clinic (witnessed dosing) at the Week 6 visit, following a meal.

- Dispense study drug

- NASH Biomarkers
- Draw blood samples for PK analysis

### 7.3.4 Week 8: Study Day 57 (±2 days)

The following procedures and assessments will be performed in addition to those listed in Section 7.3.

- Perform laboratory tests:
  - Lipid panel
  - Serum insulin
  - Plasma glucose
- Dispense study drug

### 7.3.5 Week 10: Study Day 71 (±2 days)

The following procedures and assessments will be performed in addition to those listed in Section 7.3.

- Dispense study drug

### 7.3.6 Week 12: Study Day 85 (±2 days, except MRI-PDFF, ±5 days)

The following procedures and assessments will be performed in addition to those listed in Section 7.3.

- Perform laboratory tests
  - Lipid panel
  - ACTH (morning 8:00–AM ±1 hour)
  - Serum cortisol (morning–8:00 AM ±1 hour)
  - Serum aldosterone
  - HbA1c
  - Plasma insulin
  - Plasma glucose
- NASH biomarkers (Table 5)
- Other Biomarker Assessment
  - Glucocorticoid-receptor activity marker
- Perform MRI-PDFF (Day 85±5 days)

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

Patients who discontinue the study drug before the end of the Treatment Period (12 weeks) will be asked to complete an ET visit at the time of the last dose of study drug (or soon thereafter). The following procedures and assessments will be performed in addition to those listed in Section 7.3.

- Perform laboratory tests
  - Lipid panel

  - ACTH (morning 8:00–AM ±1 hour)
  - Serum cortisol (morning 8:00–AM ±1 hour)
  - Serum aldosterone
  - HbA1c
  - Serum insulin
  - Plasma glucose
  - NASH biomarkers (Table 5)
- Perform MRI-PDFF (patients with ≥6 weeks of treatment only)
- Other Biomarker Assessment
  - Glucocorticoid-receptor activity marker

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

For patients who complete 12 weeks of treatment or for patients who discontinue early from the study drug, the Follow-Up visit will be conducted 28±5 days after their last dose of study drug The following procedures and assessments will be performed in addition to those listed in Section 7.3.

- Perform laboratory tests:
  - Lipid panel
  - Serum insulin
  - Plasma glucose

### 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 Study

Safety results collected during the study (e.g., AEs, laboratory test 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, a safety assessment committee will monitor the safety findings on a regular basis to protect the safety and ethical interests of patients. The details of the safety monitoring will be specified in a safety surveillance plan.

In addition, an IDMC will be established to conduct periodic reviews of data to ensure the safety of patients (see Section 5.10).

## 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 AE, regardless of seriousness, 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 or 4 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 7 should be used to evaluate the grade of severity for the AE.

**Table 7 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 8. 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 assess 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 8 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 listed on the cover page 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:

Covance Pharmacovigilance & Drug Safety Services

Phone: 1 888-724-4908

Fax: 1 888-887-8097

Email: SAEintake@covance.com

### 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 5.3.3.

## 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 listed on the cover page.

# 9 STATISTICAL METHODS

## 9.1 Analysis Populations

The analysis populations are defined in Table 9.

**Table 9 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 at least 1 dose of study drug and remain in the trial for at least 6 weeks. If a patient in the EE Population does not have at least 1 post-Baseline efficacy assessment for a particular efficacy endpoint, that patient will be excluded from the analysis of that endpoint. |
| PK Population | All patients who have evaluable PK data. |

Abbreviations: ICF, informed consent form; 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.

## 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 relative change in liver fat content from Baseline to Week 12. For each test, the null hypothesis is that there is no difference between miricorilant and placebo in relative change in liver fat content. The alternative hypothesis is that there is a difference between groups. Each of the 2 hypotheses will be assessed at a 2-sided $\alpha$=0.05 significance level with no adjustment to $\alpha$ for multiplicity.

## 9.4 Sample Size

The planned sample size is approximately 40 patients/group or approximately 120 subjects randomized 1:1:1 across 2 miricorilant treatment groups and one placebo group. The sample size calculation assumes that the SD for change in LFC due to treatment will be comparable to that observed in Patel et al. 2016, where an SD of 33% was reported, and in Harrison et al. 2019, where the SD was not reported but can be estimated from confidence intervals to be about 28%. A slightly more conservative estimate of 35% is assumed for the calculation here. Assuming that placebo patients experience a reduction in LFC of 10%, 34 patients per group affords 80% power to detect a significant difference at the $\alpha$=0.05 level between either miricorilant dose group and placebo as long as the miricorilant group achieves a 35% or greater reduction in LFC. Assuming

that up to 10% of patients may drop out prior to the Week 12 MRI-PDFF assessment, the required sample size increases to 38 patients per group or 114 total patients. The sample size has been rounded up to 40 patients per group, or 120 total patients, for convenience. The sample size estimate has 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. Summaries 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

Each dose of miricorilant will be compared with placebo on the key efficacy endpoint: the relative change from Baseline in LFC assessed by MRI-PDFF, where relative change is defined as 100 × (LFC at Week 12–LFC at Baseline)/LFC at Baseline. The primary analysis will use a nonparametric, rank analysis of covariance (ANCOVA) that incorporates Baseline LFC as a covariate; treatment group (2 dose levels of miricorilant and placebo) and diabetes status (stratification factor) as factors; and rank relative change in LFC as the response variable. P-values for the comparisons of each miricorilant dose group to placebo will be derived from linear contrasts. The Hodges-Lehmann method will be used to estimate the median differences between groups and their 95% confidence intervals (CIs). P-values from the comparisons will not be adjusted for multiplicity.

The primary analysis population is the EE Population. A sensitivity analysis will be conducted in the mITT Population.

Another sensitivity analysis of the primary endpoints will be performed that requires fewer assumptions than the primary analysis. The sensitivity analysis will employ 2 Wilcoxon rank-sum tests to compare each of the miricorilant dose groups to placebo; that is, one test will compare 600 mg miricorilant to placebo and another will compare 900 mg miricorilant to placebo.

The relative change in LFC in each treatment group will be summarized by the median and 25$^{th}$ and 75$^{th}$ percentiles.

### 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

The secondary efficacy endpoints will be analyzed using the EE Population unless otherwise specified.

A rank ANCOVA similar to the primary analysis will be used to test for evidence of a dose-response among the 2 miricorilant dose levels. Like the primary analysis, the model will include rank Baseline LFC as a covariate, diabetes status as a factor, and rank relative change in LFC as the response variable. But in contrast to the primary analysis, the dose-response model will not include the placebo group; that is, the treatment factor will include only the 2 dose levels of miricorilant. The two miricorilant dose groups will be compared to each other using linear contrasts. The Hodges-Lehmann method will be used to estimate the median differences between dose levels and their 95% CIs. Significant differences between groups will be taken as evidence of a dose-response relationship. Dose-response will also be assessed graphically using boxplots of the relative change in MRI-PDFF for each treatment group.

A set of 3 Cochran-Mantel-Haenszel (CMH) tests – one for each pairwise comparison of treatment groups – will be used to evaluate the secondary endpoint of the proportion of patients achieving a relative reduction in LFC of ≥30% by Week 12. Each CMH test will be stratified by diabetes status. A p-value will be reported for each test along with an estimate of the common relative risk of achieving a ≥30% reduction in LFC. Each relative risk estimate will be accompanied by a 95% CI. The percentage of patients in each group who achieve a ≥30% reduction in LFC will be presented along with a 95% CI.

The absolute change in LFC from Baseline to Week 12 will be assessed using a parametric ANCOVA model with Baseline LFC as a covariate, diabetes status and treatment group as factors, and the arithmetic difference between LFC at Week 12 and Baseline as the response variable. Linear contrasts from the model will compare each of the 2 dose levels of miricorilant to placebo. A similar ANCOVA that excludes the placebo group will be used to assess dose-response in absolute LFC change. A linear contrast from the model will compare the 2 doses of miricorilant to each other. The least squares means and associated confidence intervals derived from each model will be reported.

Other continuous secondary endpoints that are measured more than once during treatment will be analyzed using linear mixed models for repeated measures (MMRM). These endpoints include the change in AST, ALT, GGT, pro-C3, and ELF score and each of its components (TIMP-1, PIIIN, and hyalauronic acid). Restricted maximum likelihood (REML) estimation will be used. Each MMRM model will include Baseline LFC as a covariate; diabetes status, treatment, visit, and treatment by visit interaction as fixed effects; and patient within treatment group as a random effect. Comparisons of each miricorilant group to placebo and to each other will be based on the estimates from the model.

### 9.5.7 Analyses of Exploratory Endpoints

The proportion of subjects achieving a relative reduction in LFC of ≥50%, and the proportion with a complete resolution, will be analyzed using CMH tests analogous to those used to evaluate the secondary endpoint of the proportion of patients achieving a relative reduction of ≥30%.

Analyses of continuous endpoints, such as the change in ACTH, serum cortisol, and serum aldosterone from Baseline to Week 12, will be analyzed using parametric ANCOVA models with Baseline LFC as a covariate, diabetes status (stratification factor) and treatment group as factors, and the arithmetic difference between the endpoint at Week 12 and Baseline as the response variable. Changes in HbA1c and fasting blood glucose within patients with diabetes will employ pairwise Wilcoxon rank-sum tests to compare treatment groups. A similar strategy will be used to compare groups on the change from Baseline in blood pressure among patients with high blood pressure.

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

### 9.5.8 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 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, vital sign measurements, and ECG interval results will be summarized as changes from Baseline by parameter by treatment and visit using descriptive statistics. Categorical laboratory results may also be summarized using shift tables.

### 9.5.9 Pharmacokinetic Analysis

The PK data obtained from the PK analyses, 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 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).

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 and/or 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 Investigator 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, and clinic charts; the Investigator's patient study files; results of diagnostic tests, including laboratory tests and ECGs). All source data should be attributable, legible, contemporaneous, original, accurate, and completed. Changes to source data should be traceable, should not obscure the original entry, and should be explained, if necessary.

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

### 11.3.2 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 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 CRF data entry at the investigator site must obtain Investigator or designee's authorization.

### 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.

## 11.4 Sample Collection, Preparation, and Shipping

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

## 11.5 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.

## 11.6 Clinical Supplies

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

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

### 11.6.2 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.

### 11.6.3 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.

#### 11.6.3.1 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.

#### 11.6.3.2 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.

### 11.7 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. 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 Post-trial Care

Not applicable.

### 11.9 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 may be implemented.

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.

Corcept 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.

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.

## 11.10 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.

## 11.11 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.

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# 13 APPENDICES

## Appendix A: Schedule of Activities

### Table 10 Schedule of Activities

| Assessment | Screening Days -42 to -1 [a] | Baseline Day 1 | Treatment Period | | | | | | ET [b] | Follow-Up 28±5 days after last dose of study drug |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Week 2 | Week 4 | Week 6 | Week 8 | Week 10 | Week 12 | | |
| | | | Day 15 ±2 days | Day 29 ±2 days | Day 43 ±2 days | Day 57 ±2 days | Day 71 ±2 days | Day 85 ±2 days | | |
| Informed consent [c] | X | - | - | - | - | - | - | - | - | - |
| Inclusion/exclusion criteria [c] | X | - | - | - | - | - | - | - | - | - |
| Medical history and prior medications [d] | X | - | - | - | - | - | - | - | - | - |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X |
| Record AEs [d] | X | X | X | X | X | X | X | X | X | X |
| Demographics | X | - | - | - | - | - | - | - | - | - |
| AUDIT | X | - | - | - | - | - | - | - | - | - |
| Serum pregnancy test [e] | X | - | - | - | - | - | - | - | - | - |
| Urine pregnancy test [e] | - | X | X | X | X | X | X | X | X | X |
| FSH test [f] | X | - | - | - | - | - | - | - | - | - |
| Physical examination [g] | X | X | X | X | X | X | X | X | X | X |
| Height [h] | X | - | - | - | - | - | - | - | - | - |
| Weight [h] | X | X | X | X | X | X | X | X | X | X |
| Waist circumference | X | - | - | - | - | - | - | - | - | - |
| Vital signs (including orthostatic vital signs) | X | X | X | X | X | X | X | X | X | X |
| 12-lead resting ECG (in triplicate) [i] | X | X | X | X | X | X | X | X | X | X |
| FibroScan [j] | X | - | - | - | - | - | - | - | - | - |
| MRI-PDFF [k] | X | - | - | - | - | - | - | X | X | - |
| Randomization | - | X | - | - | - | - | - | - | - | - |

| Assessment | Screening Days -42 to -1 [a] | Baseline Day 1 | Treatment Period | | | | | | ET [b] | Follow-Up 28±5 days after last dose of study drug |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Week 2 | Week 4 | Week 6 | Week 8 | Week 10 | Week 12 | | |
| | | | Day 15 ±2 days | Day 29 ±2 days | Day 43 ±2 days | Day 57 ±2 days | Day 71 ±2 days | Day 85 ±2 days | | |
| Study drug dispensing | - | X | X | X | X | X | X | - | - | - |
| Study drug adherence | - | - | X | X | X | X | X | X | X | - |
| Dose diary provided | - | X | - | - | - | - | - | - | - | - |
| Dose diary (assessed and returned to patient) | - | - | X | X | X | X | X | X | - | - |
| Virus screen (HIV, HCV, HBV) | X | - | - | - | - | - | - | - | - | - |
| Hematology with platelet and WBC differential [l] | X | X | X | X | X | X | X | X | X | X |
| Chemistry, fasting [l] | X | X | X | X | X | X | X | X | X | X |
| Plasma glucose, fasting [l] | - | X | - | X | - | X | - | X | X | X |
| Serum insulin, fasting [l] | - | X | - | X | - | X | - | X | X | X |
| HbA1c [l] | X | X | - | - | - | - | - | X | X | - |
| Lipid panel, fasting [l] | X | X | - | X | - | X | - | X | X | X |
| Prothrombin time/INR [l] | X | X | - | - | - | - | - | - | - | - |
| ACTH (morning 8:00–AM±1 hour) [l] | - | X | - | - | - | - | - | X | X | - |
| Serum cortisol (morning–8:00 AM±1 hour) [l] | - | X | - | - | - | - | - | X | X | - |
| Serum aldosterone [l] | - | X | - | - | - | - | - | X | X | - |
| NASH biomarkers [m] | - | X | - | - | X | - | - | X | X | - |
| Glucocorticoid-receptor activity marker | - | X | - | - | - | - | - | X | X | - |
| PK samples [n] | - | - | - | - | X | - | - | - | - | - |

Abbreviations: ACTH, adrenocorticotropic hormone; AE, adverse events; AUDIT, Alcohol Use Disorders Identification Test; ECG, electrocardiogram; ET, early termination; FSH, follicle-stimulating hormone; HbA1c, glycated hemoglobin; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INR, international

normalized ratio; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NASH, nonalcoholic steatohepatitis; PK, pharmacokinetics; WBC, white blood cell count.

a. If a patient continues to be eligible following laboratory tests at Screening, MRI-PDFF will be performed during a separate visit.
b. 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.
c. Confirm informed consent was obtained and patient meets inclusion/exclusion criteria prior to randomization at Baseline Day 1 Visit.
d. 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.
e. Serum and urine pregnancy tests will be completed on all women of childbearing potential. If urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test.
f. FSH will be completed on women who have a 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 postmenopausal female.
g. Comprehensive physical examinations will be performed at Screening, Baseline, Early Termination, and Follow-up. Symptom-directed physical examinations will be performed at the other study visits. Genitourinary, rectal, and breast examinations are not required.
h. BMI will be autocalculated from the EDC database based on height and weight measurements.
i. At Baseline, 12-lead resting ECG (in triplicate) will be performed both before dosing and 2 hr ±15 min after dosing.
j. Results from FibroScans performed within 3 months of Screening are acceptable.
k. MRI-PDFF to be performed at Screening and at Week 12 (Day 85 ±5 days). The assessment should also be completed at the ET visit only if the patient had at least 6 weeks of treatment.
l. All clinical laboratory samples will be collected when the patient is fasting (at least 8 hours); ACTH and serum cortisol tests will be completed in the morning–8 AM ±1 hour).
m. NASH Biomarkers include AST, ALT, GGT, pro-C3, ELF score and its components (hyaluronic acid, TIMP-1, PIIINP).
n. Patients will be required to take their dose of study drug on the day of their Week 6 visit in the clinic (witnessed dosing).

## Appendix B: Summary of Changes

Significant changes in Amendment 2 of the protocol compared with the Amendment 1 are summarized below. Additional details are provided in Table 11; deleted text is shown as a strikethrough and new text is shown in bold font. Minor editorial or stylistic changes made for consistency or correction of typographical errors are not redlined nor summarized.

- Added inclusion criterion (#5) to allow enrollment of patients on stable doses of lipid-modifying therapies for at least 3 months prior to Screening.
- Updated exclusion criterion (#15) to align with prohibited medications and permitted concomitant medications requiring caution.
- List of permitted concomitant medications requiring caution updated to align with the list of prohibited medications.
- Cautionary measures for a list of permitted concomitant medications were added.
- Added instructions for orthostatic vital signs measurement.
- Clarified window for post-dosing ECG assessment at Baseline.
- Frequency of creatine kinase assessment updated (occurs at all visits when the chemistry assessment is performed).

## Table 11 Summary of Changes in Protocol CORT118335-860 Amendment 2

| Section | Revisions |
|---|---|
| Global Changes | For the version of the protocol, changed "Amendment 1" to "Amendment 2" and changed the date from 14 October 2020 to 07 December 2020. |
| Synopsis | Updated text in synopsis to align with changes in the body of the protocol.<br>Expanded the list of key exclusion criteria in the synopsis (the following exclusion criteria were previously listed in the body of the protocol only).<br>• **Women who are pregnant, planning to become pregnant, or are lactating.**<br>• **Have a BMI <18 kg/m$^2$.**<br>• **Are currently using any medications prohibited due to the potential for drug-drug interactions (DDI) with study treatments Prohibited medications (see Section 5.4.3) must be discontinued at least 5 half-lives prior to a patient receiving their first study treatment. Administration of concomitant medications (see Section 5.4) are at the discretion of the Investigator and/or the Corcept Medical Monitor.**<br>…..<br>• **Have abnormal screening laboratories:**<br>**a. AST >5× upper limit of normal (ULN)**<br>**b. ALT >5× ULN**<br>**c. Estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73 m$^2$**<br>**d. Creatine kinase >3×ULN** |
| 4.1 Inclusion Criteria | Added inclusion criterion.<br>**5. Patients who are taking lipid-modifying therapies must be on stable doses for at least 3 months prior to Screening and unlikely to change the dose during the study (for patients taking statin medications, please see additional restrictions in exclusion criterion #15).** |
| 4.2 Exclusion Criteria | Updated exclusion criterion.<br>~~15. Use any of the following lipid-modifying therapies*:~~<br>~~a. Fibrates (except stable doses of fenofibrate for at least 3 months prior to Screening), niacin, proprotein convertase subtilisin/kexin type 9 inhibitors, and bile acid sequestrants.~~<br>~~b. All statins except stable doses of atorvastatin (up to 20 mg) , rosuvastatin (up to 10 mg), and pravastatin (up to 20 mg) for at least 6 weeks prior to Screening are allowed.~~<br>~~*Stable doses for at least 3 months prior to Screening of fish oils (omega-3 fatty acids, eicosapentaenoic acid, and docosahexaenoic acid) and ezetimibe are allowed.~~<br>**15. Are currently taking a statin other than stable of the following: lovastatin (up to 20 mg), pravastatin, pitavastatin, simvastatin (up to 10 mg), atorvastatin (up to 20 mg), or fluvastatin (up to 20 mg). A stable dose is defined as no changes in the dose in the last 3 months prior to Screening.**<br>Added the following exclusion criterion.<br>**17. Are currently using a medication such as digoxin with an increased risk for toxicity in the event of electrolyte changes.** |
| 4.4.1 Early Patient Discontinuation of Study Drug | Deleted bullet.<br>Study drug may be discontinued in the event of any of the following occurrences:<br>~~• Lack of efficacy.~~ |

<table>
<tr><th>Section</th><th>Revisions</th></tr>
<tr><td>5.4.1 Permitted Concomitant Meds</td><td>Edited text for clarity.<br>All medications (other than study treatments) administered ~~within~~ 28 days before study entry (i.e., after a patient signs the ICF) and during the study must be listed on the concomitant medications eCRF.<br>Table 3 Permitted Concomitant Medications, clarified restrictions for lipid-modifying drugs.<br>Third row:
<table>
<tr><td>Lipid-~~lowering~~modifying drug</td><td>No ~~increases~~ changes in current dose allowed from 6 weeks before Baseline through the Follow-up Visit.<br>Do not add new lipid~~-lowering~~modifying medications without prior consultation with the Corcept Medical Monitor.</td></tr>
</table></td></tr>
<tr><td>5.4.2 Permitted Concomitant Therapy Requiring Caution</td><td>Edited the list of permitted concomitant therapy to align with the list of prohibited medications in Section 5.4.3 and based on current information about miricorilant.<br>Permitted concomitant medications to be used with caution from 1 week before Baseline through the Follow-up Visit are as follows:<br>• Moderate ~~inhibitors or~~ inducers of CYP2C19.<br>~~• Substrates metabolized predominantly by CYP3A4, CYP2C8, and/or CYP2C9 with a narrow therapeutic index.~~<br>• Strong inhibitors of CYP3A4, CYP2C8, and/or CYP2C9~~, and/or P-glycoprotein~~.<br>• Prescription or over-the-counter medications that are a substrate for breast cancer resistance protein (BCRP) or uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) and are not prohibited with BCRP and/or UGT1A1 inhibitors and for which an acceptable dose modification can be implemented to allow coadministration with miricorilant.<br>• Medications that carry a possible risk for QT prolongation.<br>Table 4 Cautionary Measures for Permitted Concomitant Medications, added cautionary measures for a list of permitted concomitant medications.
<table>
<tr><th>Medication</th><th>Cautionary Actions</th></tr>
<tr><td>Simvastatin</td><td>Simvastatin should be dosed in the evening as per its label and separated from the morning dose of miricorilant by 12 hours.</td></tr>
<tr><td>Atorvastatin</td><td>Atorvastatin should be dosed in the evening and separated from the morning dose of miricorilant by 12 hours.</td></tr>
<tr><td>Fluvastatin</td><td>Fluvastatin should be dosed in the evening as per its label and separated from the morning dose of miricorilant by 12 hours.</td></tr>
<tr><td>Glyburide</td><td>Fingerstick blood glucose monitoring may need to be increased from Baseline to Week 2.</td></tr>
<tr><td>Losartan</td><td>Dosing should be separated from miricorilant by 12 hours.<br>Blood pressure monitoring may need to be increased from Baseline to Week 2.</td></tr>
</table></td></tr>
<tr><td>5.4.3 Prohibited Medications</td><td>Edited the list of prohibited medications to align with Section 5.4.2 and based on current information about miricorilant.<br>The following medications are prohibited during treatment with miricorilant in this study:<br>….<br>• Prescription or over-the-counter medications that are ~~strong inducers or~~ moderate and strong inhibitors of CYP2C19.<br>• Prescription or over-the-counter medications that are strong inducers of CYP2C19.<br>….</td></tr>
</table>

| Section | Revisions |
|---|---|
| | • Prescription or over-the-counter medications that are a substrate for BCRP or UGT1A1 **and have clinically significant in vivo drug-drug interactions with BCRP and/or UGT1A1 inhibitors and for which an acceptable dose modification is not an option.** |
| 6.4.1 Physical Examination and Vital Signs | Added instructions for orthostatic vital signs.<br>*Paragraph 4:*<br>**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.** |
| 6.4.5.1 Laboratory Parameters | Table 5 Clinical Laboratory Variables Evaluated During the Study, edited assessment for creatine kinase to clarify that it will be performed at all visits when the chemistry assessment is performed.<br>Creatine kinase ~~(Screening only)~~ |
| 7.2 Baseline (Day 1) | Edited assessments to include window for ECG assessment post dosing.<br>Perform 12-lead resting ECG (in triplicate) before **dosing** and **2 hr ±15 min** after dosing |
| 7.3.3 Treatment Period Week 6: Study Day 43 (±2 days) | Clarified that for the PK assessment at Week 6 dosing will be performed following a meal.<br>The following procedures and assessments will be performed in addition to those listed in Section 7.3. For the PK analysis, all patients will be required to take their dose in the clinic (witnessed dosing) at the Week 6 visit**, following a meal**. |
| 8.11 Procedures for Reporting a Serious Adverse Event | Clarified that SAEs should be reported to designated safety contact in addition to the medical monitor; included reporting information in the case of SAEs.<br>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 listed on the cover page **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).<br>**SAE reporting details are provided below:**<br>**Covance Pharmacovigilance & Drug Safety Services**<br>**Phone: 1 888-724-4908**<br>**Fax: 1 888-887-8097**<br>**Email: SAEintake@covance.com** |
| 9.5.6 Analysis of the Secondary Efficacy Endpoints | Corrected the number of miricorilant dose groups.<br>*Paragraph 2:*<br>A rank ANCOVA similar to the primary analysis will be used to test for evidence of a dose-response among the ~~3~~ **2** miricorilant dose levels. Like the primary analysis, the model will include rank Baseline LFC as a covariate, diabetes status as a factor, and rank relative change in LFC as the response variable. But in contrast to the primary analysis, the dose-response model will not include the placebo group; that is, the treatment factor will include only the ~~3~~ **2** dose levels of miricorilant. ~~Each~~ **The two** miricorilant dose group**s** will be compared to each other using linear contrasts. The Hodges-Lehmann method will be used to estimate the median differences between dose levels and their 95% CIs |
| Appendix A | Edited HbA1c assessment in Schedule of Activities to clarify that it is not required for the patient to be fasting for this assessment.<br>HbA1c~~, fasting~~ [i]<br>Edited the footnote for ECG assessment to align with Section 7.<br>[i] At Baseline, 12-lead resting ECG (in triplicate) will be performed both before **dosing** and **2 hr ±15 min** after dosing. |

| Section | Revisions |
|---|---|
| | Clarified the footnote for MRI-PDFF assessment.<br>[k] MRI-PDFF to be performed at **Screening and at Week 12 (Day 85 ±5 days). The assessment should also be completed at the** ~~early termination~~ **ET visit** only if the patient had at least 6 weeks of treatment. ~~At the Week 12 visit, the assessment can be performed on Day 85±5 days.~~ |