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

STATISTICAL ANALYSIS PLAN (SAP)

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)**
Study Protocol	CORT118335-860
Phase	2a
Investigational Product	Miricorilant (CORT118335)
Indication	Nonalcoholic Steatohepatitis (NASH)
Protocol Version	Amendment 2
Protocol Version (date)	07 December 2020
Sponsor	Corcept Therapeutics Incorporated 149 Commonwealth Drive Menlo Park, California 94025 USA (650) 327-3270
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Confidentiality Statement

APPROVAL SHEET

STATISTICAL ANALYSIS PLAN

CORT118335-860: A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Efficacy, and Pharmacokinetics of Miricorilant in Patients with Presumed Nonalcoholic Steatohepatitis (NASH)

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CRO REVIEW SHEET

STATISTICAL ANALYSIS PLAN

CORT118335-860: A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Efficacy, and Pharmacokinetics of Miricorilant in Patients with Presumed Nonalcoholic Steatohepatitis (NASH)

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACTH	adrenocorticotropic hormone
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
AUDIT	Alcohol Use Disorders Identification Test
BMI	body mass index
CI	confidence interval
COVID-19	coronavirus disease of 2019
CSR	clinical study report
CTCAE	common terminology criteria for adverse events
DBP	diastolic blood pressure
ECG	electrocardiogram
eCRF	electronic case report form
ELF	enhanced liver fibrosis
GGT	gamma-glutamyl transferase
HbA1c	glycated hemoglobin
HOMA-IR	homeostatic model assessment for insulin resistance
ICH	International Council for Harmonisation
ID	identifier
ITT	intent-to-treat
IWRS	interactive web response system
LFC	liver fat content
LLOQ	lower limit of quantification
MedDRA	medical dictionary for regulatory activities
MRI-PDFF	magnetic resonance imaging-proton density fat fraction
NASH	nonalcoholic steatohepatitis
PIIINP	type III procollagen
PK	pharmacokinetic
pro-C3	propeptide of type III collagen

Abbreviation	Definition
PT	preferred term
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SI	Système International
SOC	system organ class
SDTM	Study Data Tabulation Model
TEAE	treatment-emergent adverse event
TIMP-1	tissue inhibitor of metalloproteinases-1
ULOQ	upper limit of quantification
WHO	World Health Organization

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1 INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis populations and endpoints, outlines the timing of statistical analyses, and provides a comprehensive description of statistical analyses to be implemented to assess the clinical efficacy and safety of protocol CORT118335-860, amendment 2, dated 07 December 2020: A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Efficacy, and Pharmacokinetics of Miricorilant in Patients with Presumed Nonalcoholic Steatohepatitis (NASH).

This SAP will be finalized before database lock and prior to data analysis to provide full details of statistical analysis to be presented in the clinical study report (CSR). Any changes between the statistical methods provided in the clinical study protocol and this SAP will be explained herein; any changes or deviations from this SAP relative to the final analysis will be fully documented in the CSR. Minor changes or deviations from the templates for tables, figures, and listings need not be documented in the CSR.

2 STUDY OVERVIEW

2.1 Overall Design

This is a Phase 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, pharmacokinetics (PK), and preliminary efficacy of miricorilant.

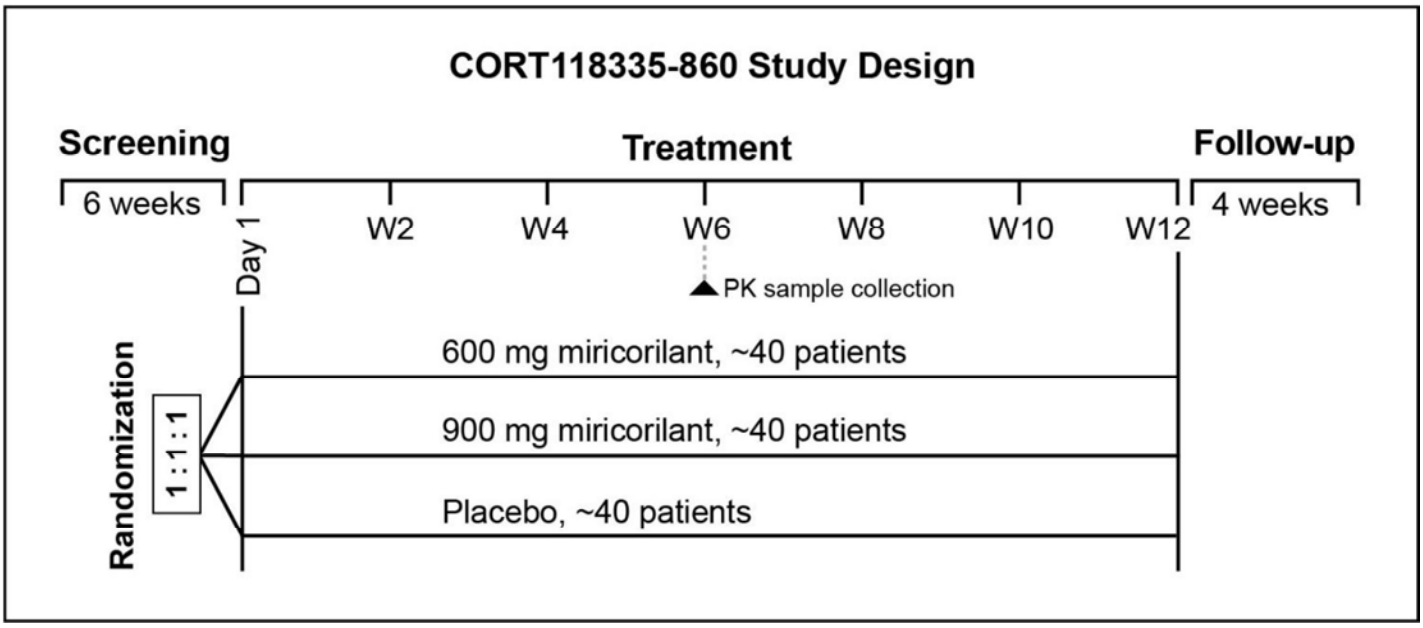
The study consists of the following study periods:

- Screening Period: up to 6 weeks
- Treatment Period: Day 1 (Baseline) to Week 12
- Follow-up Period: 4 weeks after last study dose (Week 16)

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. Randomization will be stratified by the presence or absence of diabetes.

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

Figure 1 CORT118335-860 Study Design



Abbreviation: PK, pharmacokinetics; W, week.

3 STUDY OBJECTIVES

3.1 Primary Efficacy Objective

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

3.2 Secondary Objective

- 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.

3.3 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.

3.4 Safety Objective

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

3.5 Pharmacokinetic Objective

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

4 STUDY ENDPOINTS

4.1 Primary Efficacy Endpoint

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.

4.2 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 aspartate aminotransferase (AST), alanine aminotransferase (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.

4.3 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.

4.4 Safety Endpoints

The following endpoints will be assessed for miricorilant versus placebo:

- Incidence of treatment-emergent adverse events (TEAEs), adverse events (AEs), and Serious TEAEs.
- 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 electrocardiogram (ECG) parameters.

5 SAMPLE SIZE CONSIDERATIONS

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 standard deviation (SD) for change in liver fat content (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 α=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.

6 ANALYSIS POPULATIONS

6.1 All Enrolled Population

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

6.2 Safety Population

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

6.3 Intent-To-Treat (ITT) Population

The ITT population comprises all patients who are randomized to the study. Efficacy data will be summarized based on the ITT population.

7 DEFINITIONS, COMPUTATIONS AND CONVENTIONS

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

7.1 Definitions

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

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

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

7.2 Reporting Conventions

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

- Mean, median, 25th percentile, and 75th percentile values will be formatted to 1 more decimal place than the measured value. Standard deviation values will be formatted to 2 more decimal places than the measured value; minimum and maximum values will be presented to the same number of decimal places as the measured value.
- Percentages will be rounded to 1 decimal place. Number and percentage values will be presented as xx (xx.x%).
- Listings will be sorted for presentation in order of patient identifier (ID), and date of procedure or event.
- Analysis and summary tables will have the analysis population sample size (i.e., number of patients).
- Laboratory data will be reported using Système International (SI) units
- For by-visit observed data analyses, percentages will be calculated based on the number of patients with non-missing data as the denominator unless otherwise specified.

- For other continuous endpoints, the summary statistics will include mean, standard deviation, median, 25th percentile, 75th percentile, and range (minimum and maximum).
- For categorical endpoints, the summary statistics will include frequency counts and percentages.
- Medical history and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA v 23.0. Adverse event severity will be evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v.5.0).
- Prior therapies and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary and summarized by Anatomical Therapeutic Chemical (ATC) therapeutic subgroup and preferred drug names.
- For continuous values (clinical laboratory values) that are not able to be determined due to being less than the lower limit of quantification (LLOQ) or higher than the upper limit of quantification (ULOQ), the value will be assigned to one unit lower than the LLOQ or one unit higher than the ULOQ for any analyses performed. The original value will be displayed in any listings provided.

7.3 Conventions for Dates

Conventions for calculations with dates are as follows:

- Dates will be stored as numeric variables in the SAS analysis files and reported in DDMMMYYYY format (i.e., the Date9. date format in SAS).
- Dates recorded in comment fields will not be imputed or reported in any specific format.
- Intervals that are presented in weeks will be transformed from days to weeks by using the following conversion formula, and rounding to 1 decimal place:
  - WEEKS = DAYS / 7
  - MONTHS = DAYS / 30.4375
  - YEARS = DAYS / 365.25

Detailed rules for imputation of missing/partially missing dates for adverse events and prior/concomitant medications/procedures are provided in Section 12.1.

7.4 Treatment Group Presentation

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

7.5 Handling of Missing Data

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

Missing dates or partially missing dates will be imputed conservatively for adverse events and prior/concomitant medications/procedures. Specific rules for handling of missing or partially

missing dates for date of birth, adverse events, and prior/concomitant medications/procedures are provided in Section 12.1.

7.6 Analysis Visit Windows

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

Table 1 Analysis Visit Windows for Assessments

Visit Name	Start Day	Target Day	End Day
Baseline	—	1	—
Week 2	2	15	22
Week 4	23	29	36
Week 6	37	43	50
Week 8	51	57	64
Week 10	65	71	78
Week 12	79	85	92
Follow-up	> Study day of last dose of study drug	Initial visit after end of treatment	
Additional Follow-up	> Study day of last dose of study drug	Second visit after end of treatment	
Note: Any unscheduled and early termination visits that occur after the last dose of study drug will be classified in the follow-up period.			

8 TIMING OF ANALYSES

8.1 Interim Analysis

No interim analyses are planned for this study.

8.2 Final Analyses and Reporting

All planned analyses described in the SAP will be performed after the study has completed, all outstanding queries resolved, and the database has been locked.

9 STATISTICAL METHODS

9.1 General Statistical Consideration

Statistical analyses will be reported with tables, figures, and listings, presented in rich text format, and using recommended ICH numbering. Output specifications for all tables, figures, and listings will be in conformance with guidelines specified by the ICH of the Electronic Common Technical Document Specification (Apr 2003).

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

In general, continuous variables will be summarized by the number of patients with non-missing data, mean, SD, median, 25th percentile, 75th percentile, minimum, and maximum values. Categorical variables will be summarized by the number and percentage of patients in each category.

9.2 Patient Disposition

Screen failure information is collected in an interactive web response system (IWRS), not on the eCRF and it is not be incorporated into the Study Data Tabulation Model (SDTM) database. Information on participant screening will be presented in terms of the overall number of participants screened, number of patients who are screen failures, reasons for screen failures, and the number of participants in screening.

Participant disposition will show the number of patients who have been enrolled, in each analysis population, took study drug, discontinued treatment, discontinued from the study, reasons for discontinuations, completed 12 weeks of study treatment, completed the study, and completed the follow-up study visit.

Completion of the follow-up study visit is defined as completing the date of visit eCRF for the follow-up visit.

9.3 Protocol Deviations

Protocol deviations will be categorized as important or other according to the protocol deviation specification document. A by-patient listing of important protocol deviations will be provided for the ITT population.

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

9.4 Demographic and Baseline Characteristics

The following demographic characteristics will be presented for the Safety population in listing, and summarized by treatment and overall:

- Age at informed consent (continuous and categorical variable: < 30, 30-50, and > 50 years) will be summarized
- Sex
- Of childbearing potential (Yes/No)
- Ethnicity
- Race
- Height
- Weight
- Body mass index (BMI) (continuous and categorical variable: obesity class 1 (30-34.9 kg/m^2), obesity class 2 (35-39.9 kg/m^2), extreme obesity class 3 ($\geq$ 40 kg/m^2))
- Alcohol Use Disorders Identification Test (AUDIT) score

BMI will be calculated as: weight (kg) / [height (cm) / 100]^2. The imputation rules for missing or partial diagnosis dates are described in Section 12.1.

9.5 Medical History

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

9.6 Prior and Concomitant Medications and Subsequent Therapies

Medications will be coded using the WHO Drug Global B3 version September 2019 or above. Medications entered on the eCRF will be mapped to ATC drug class (level 4) and generic drug name.

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

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

9.7 Extent of Exposure and Study Drug Compliance

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

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

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

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

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

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

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

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

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

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

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

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

9.8 Efficacy Analyses

Due to observations related to safety, the study was terminated by the sponsor prior to completion. The sample size at the time of study termination does not support formal comparisons of the treatment groups, and therefore, no efficacy analyses specified in the protocol will be performed. Descriptive statistics for efficacy endpoints will be provided as described below.
Furthermore, no patient reached their Week 12 visit, and therefore, descriptive statistics at Week 12 will not be presented. Instead, descriptive statistics will be provided for all analysis visits up to the last non-missing visit.

9.8.1 Primary Efficacy Analysis

The primary endpoint is used to evaluate the primary objective of assessing the efficacy of each of the 2 miricorilant doses (600 mg and 900 mg) compared with placebo in in reducing liver fat content. More specifically, each dose of miricorilant will be compared with placebo on the

relative change from baseline in LFC assessed by MRI-PDFF, where for the l^{th} patient, the relative change is calculated as

$$Z_{x,l} = \left(\left(LFC_{x,l} - LFC_{bl}\right)/LFC_{bl}\right) \times 100$$

where $LFC_{x,l}$ is the LFC measured at visit x for the l^{th} patient, and LFC_{bl} is the baseline LFC for the l^{th} patient.

Descriptive statistics (mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum) will summarize the relative change from baseline to post-baseline in LFC by treatment group and overall.

9.8.1.1 Sensitivity Analyses

No sensitivity analyses will be performed.

9.8.2 Secondary Efficacy Analyses

9.8.2.1 Relative Change from Baseline in Liver Fat Content for Both Dose Levels of Miricorilant Combined vs Placebo

For the first secondary endpoint, the 2 miricorilant dose groups will be combined into a single treatment group and descriptive statistics will summarize the relative change from baseline to post-baseline in LFC by treatment group.

9.8.2.2 Responders Achieving a ≥ 30% Reduction in Liver Fat Content

The second secondary efficacy endpoint is the percentage of patients achieving a ≥ 30% reduction in the relative change in LFC from Baseline for each of the 2 miricorilant doses versus placebo. The endpoint requires calculation of the relative change in LFC as described in Section 9.8.1.

The outcome variable will be a binary variable indicating a patient as a responder, that is whether the l^{th} patient achieved a ≥ 30% reduction in LFC from baseline:

$$\theta_l = \begin{cases} 1 \text{ if } Z_{x,l} \leq -30 \\ 0 \text{ otherwise} \end{cases}.$$

where $Z_{x,l}$ is the relative change in LFC (Section 9.8.1).

A frequency table for the number of patients who have achieved a ≥ 30% reduction in LFC from baseline to post-baseline will be provided.

9.8.2.3 Absolute Change from Baseline in Liver Fat Content

Descriptive statistics will summarize the absolute (arithmetic) change from baseline in LFC by treatment group and overall post-baseline.

9.8.2.4 NASH Biomarkers

9.8.2.4.1 AST, ALT, and GGT

Separate from laboratory summaries, descriptive statistics will summarize AST, ALT, and GGT by treatment and overall at all non-missing corresponding visits associated with NASH Biomarker data collection. The change from baseline in AST, ALT, and GGT will be presented by treatment and overall at all non-missing post-baseline analysis visits.

9.8.2.4.2 Propeptide of Type III Collagen (pro-C3)

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).

Descriptive statistics will summarize pro-C3 by treatment and overall at all non-missing visits and the change from baseline in pro-C3 by treatment and overall at all non-missing post-baseline analysis visits.

9.8.2.4.3 Enhanced Liver Fibrosis (ELF) Score and Its Components

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.

Descriptive statistics will summarize the ELF score and its components by treatment and overall at all non-missing visits and the change from baseline in the ELF score and its components by treatment and overall at all non-missing post-baseline analysis visits.

9.8.3 Exploratory Analyses

9.8.3.1 Responders Achieving a ≥ 50% Reduction in Liver Fat Content

The percentage of patients achieving a ≥ 50% reduction in the relative change in LFC from baseline for each of the 2 miricorilant doses versus placebo will be determined as described in Section 9.8.2.2. A frequency table for the number of patients who have achieved a ≥ 50% reduction in LFC from baseline to post-baseline will be provided.

9.8.3.2 Proportion of Patients with Complete Resolution

Complete resolution of fatty liver is any MRI-PDFF value less than 5%. A frequency table for the number of patients who have achieved complete resolution in LFC from baseline to post-baseline will be provided. Patients with complete resolution of fatty liver by MRI-PDFF will be listed including duration on study drug, last dose date, MRI date, and duration between last dose date and MRI date.

9.8.3.3 Homeostatic Model Assessment for Insulin Resistance

HOMA-IR will be calculated by the central laboratory for each patient at each visit using the approximate formula (Matthews et al. 1985):

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

Descriptive statistics will summarize HOMA-IR by treatment group and overall for all visits and the change and percent change from baseline in HOMA-IR by treatment group and overall for all post-baseline analysis visit.

9.8.3.4 Adrenocorticotropic Hormone

ACTH will be listed by patient and visit including change from baseline.

9.8.3.5 Serum Cortisol

Like ACTH, serum cortisol will be listed by patient and visit including change from baseline.

9.8.3.6 Serum Aldosterone

Serum aldosterone will be summarized by descriptive statistics including change from baseline for all analysis visits during the treatment and follow-up period.

9.8.3.7 Other Exploratory Analyses in Patients with Diabetes or High Blood Pressure

No analyses will be performed for patients with diabetes or high blood pressure.

9.9 Safety Analyses

All safety analyses will be performed in the Safety Population. All safety data will appear in by-patient data listings. Unless specified otherwise, the categorical safety analyses will include both scheduled and unscheduled visits. No comparisons between treatment groups for safety measures will be made.

9.9.1 Adverse Events

TEAEs are defined as those AEs with onset on or after the first dose date of study drug or existing events that worsened after the first dose during the study and up to and including 28 days after the last dose of study drug, per protocol. Any AEs reported more than 28 days after the last dose of study drug will be considered post-treatment AEs.

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

Summaries that are displayed by system organ class (SOC) and preferred terms (PT) will be ordered by alphabetical orderof SOC and by descending total incidence PT nested within each system organ class. Summaries displayed by PT only will be ordered by descending total incidence of PT.

Tabular summaries with numbers and percentages of patients that have the following adverse events will be provided:

- Overview of TEAEs
- Summary of TEAEs
- Summary of TEAEs related to study drug (defined as possibly related, probably related, or related)
- Summary of TEAEs leading to discontinuation
- Summary of Serious TEAEs
- Summary of Serious TEAEs related to study drug
- Summary of Serious TEAEs leading to discontinuation
- Summary of TEAEs with fatal outcome
- Summary of TEAEs with Grade 3 or higher

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

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

9.9.2 Deaths

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

9.9.3 Clinical Laboratory Tests

All descriptive summaries of laboratory results will be based on data analyzed by the central laboratory and presented in SI units. All data will be included in by-patient data listings. Laboratory measurements identified as abnormal (i.e., outside the normal range) will also be listed separately by patient, study visit, laboratory test, unit laboratory value, normal ranges, and abnormal category (e.g. high, low, abnormal).

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

The CTCAE grading will be performed for all available laboratory parameters. The grading used for analysis will be based on the laboratory data only, without checking other data points that may be referenced in the CTCAE grading.

An evaluation of drug-induced serious hepatotoxicity (eDISH) plot will be generated. Additionally, a summary of the number of patients with liver test abnormalities will be provided for the worst value after first dose of study drug including ALT (>3xULN, >5xULN, >10xULN, and >20xULN), AST (>3xULN, >5xULN, >10xULN, and >20xULN), total bilirubin (>ULN and >2xULN), ALP (>1.5xULN), and ALT or AST >3xULN and total bilirubin (>1.5xULN and >2xULN). A listing of all patients with liver test abnormalities will be provided including all laboratory values and corresponding abnormality.

9.9.4 Vital Signs

Vital sign parameter measurements, including systolic blood pressure (SBP) and diastolic blood pressure (DBP), heart rate, respiratory rate, and body temperature, will be summarized by position (seated, supine, and standing). Descriptive statistics will be presented for results, as well as change from baseline for all post-baseline analysis visits up to and including the Follow-up visit for the Treatment and Follow-up periods.
Vital signs, including SBP, DBP, heart rate, respiratory rate and body temperature will be listed.

9.9.5 Electrocardiograms

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

Twelve-lead ECG results will be classified as “normal”, “abnormal not clinically significant”, and “abnormal clinically significant” on the eCRF. A listing of ECG results will be provided including visit, date, and interpretation results.

9.9.6 Physical Examination

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

9.9.7 Pregnancy Tests

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

9.10 Subgroup Analyses

No subgroup analyses will be performed.

9.11 COVID-19 Infection

Information regarding visits that are affected by coronavirus disease of 2019 (COVID-19) pandemic are being collected on the eCRF. A listing of visits that are affected by COVID-19

pandemic will be provided. Additionally, a listing of protocol deviations associated with COVID-19 and an AE listing of patients with a positive diagnosis of COVID-19 infection will be provided. Any additional analyses determined to be appropriate for patients impacted by the COVID-19 pandemic will be performed as deemed necessary.

10 CHANGES FROM PROTOCOL IN STUDY CONDUCT OR STATISTICAL ANALYSIS PLAN

The SAP supersedes the statistical methods described in the clinical study protocol. Analysis methods that summarize and evaluate study efficacy endpoints for statistical significance will be implemented as described in the SAP. Changes from the protocol statistical analysis include:

- Removal of the Modified Intent-to-Treat, Efficacy Evaluable, and PK populations.
- Removal of PK analysis including calculation of the PK parameters of miricorilant estimated by noncompartmental methods, summary of PK parameters, and plots of plasma concentrations of miricorilant. A PK analysis plan will not be prepared. Any reported PK data will be listed as observed.
- Removal of analyses of exploratory endpoints in patients with diabetes or high blood pressure.
- The sample size at the time of study termination does not support formal comparisons of the treatment groups, and therefore, no efficacy analyses specified in the protocol will be performed.

11 REFERENCES

E9 Statistical Principles for Clinical Trials, provided by the International Conference on Harmonization. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e9-statistical-principles-clinical-trials

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Matthews D, Hosker J, Rudenski A, Naylor B, Treacher D, Turner RC. 1985. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28(7): 412–419.

M2 eCTD: Electronic Common Technical Document Specification Appendix 7, provided by the International Conference on Harmonization. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073240.pdf

Patel J, Bettencourt R, Cui J, et al. 2016. Association of noninvasive quantitative decline in liver fat content on MRI with histologic response in nonalcoholic steatohepatitis. Therap Adv Gastroenterol. 9:692–701

Vilar-Gomez E, Chalasani N. 2018. Non-invasive assessment of non-alcoholic fatty liver disease: Clinical prediction rules and blood-based biomarkers. J Hepatol. 68(2):305–315.

12 APPENDIX

12.1 Imputation of Missing/Partially Missing Dates

For adverse events with a partial date, available date parts (year, month, and day) of the partial date will be compared with the corresponding date components of the start date and end date of the treatment-emergent period to determine if the event is treatment emergent. The following rules will be applied to impute partial dates for adverse events.

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

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

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

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

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

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

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

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

- If both Month and Day are missing, then set to December 31.
- If only Day is missing, then set to last day of the month.

If start date or end date of a medication is completely missing, no imputation is applied.

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In Person Signer Events	**Signature**	**Timestamp**
Editor Delivery Events	**Status**	**Timestamp**
Agent Delivery Events	**Status**	**Timestamp**
Intermediary Delivery Events	**Status**	**Timestamp**
Certified Delivery Events	**Status**	**Timestamp**
Carbon Copy Events	**Status**	**Timestamp**
Witness Events	**Signature**	**Timestamp**
Notary Events	**Signature**	**Timestamp**

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	8/30/2021 3:54:01 PM
Certified Delivered	Security Checked	8/31/2021 6:48:51 AM
Signing Complete	Security Checked	8/31/2021 6:49:31 AM
Completed	Security Checked	8/31/2021 6:49:31 AM
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